Cardiovascular risk assessment: the modification of blood lipids for the primary and secondary prevention of cardiovascular disease

Full guideline

Consultation Draft

June 2007

National Collaborating Centre for

Primary Care

NOTE: Please reference the page number and line number for each comment.
Citation


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Preface

(To be inserted in final document post consultation)

1 Key priorities for implementation

A number of key priority recommendations that have been identified for implementation are listed below. These recommendations are considered by the GDG to have the most significant impact on patients’ care and outcomes.

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<thead>
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<td>When considering therapy for lipid modification, all modifiable cardiovascular risk factors should be considered and their management optimised. Assessment should include evaluation of:</td>
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</table>
  * smoking status |
  * blood pressure |
  * Body Mass Index or other measure of obesity (refer to NICE Obesity guideline, No. CG43, 2006) |
  * fasting total cholesterol, LDL cholesterol, HDL cholesterol and triglycerides |
  * fasting blood glucose |
  * renal function |
  * liver function (transaminases). |
  * Secondary causes of dyslipidaemia should be considered and excluded before starting lipid therapy. This should include measurement of thyroid |
Key recommendations - primary prevention specific

For the primary prevention of cardiovascular disease (CVD) in primary care, a systematic strategy should be used to identify individuals likely to be at high risk.

Individuals should be prioritised for assessment based upon a prior estimate of their CVD risk. This should be calculated using the recommended risk equation utilising CVD risk factors recorded in their primary care electronic medical records or estimates where these are missing, including:

- age
- sex
- smoking status
- blood pressure
- total cholesterol
- HDL cholesterol


a) 10-year coronary heart disease (CHD) risk (CHD death, non-fatal CHD including silent MI, angina, coronary insufficiency (acute coronary syndrome))

b) 10-year risk of fatal and non-fatal stroke, including transient ischaemia.

c) CVD risk = a+b.

People should receive information about their absolute risk of CVD, and about the absolute risk (including benefits and adverse events) of an intervention over a 10-
year period in a format that:

- presents individualised risk and benefit scenarios
- presents the absolute risk of events numerically
- uses appropriate graphical and written formats.

Statin therapy is recommended as part of the management strategy for the primary prevention of CVD in adults who have a 20% or greater 10-year risk of developing CVD. This level of risk should be estimated using the recommended CVD risk equations or by clinical assessment in people for whom these are not available or appropriate (for example, people aged over 75 years).

Simvastatin 40 mg or pravastatin 40 mg, or a drug of comparable effectiveness and acquisition cost, is recommended as the treatment.

Key recommendations - secondary prevention specific

Statin therapy is recommended for adults with clinical evidence of CVD (NICE technology appraisal 94, ‘Statins for the prevention of cardiovascular events’ 2007)

Treatment should be initiated with simvastatin 40 mg for patients in the following groups:

- after myocardial infarction, or acute coronary syndrome or new-onset angina
- with chronic stable angina
- after ischaemic stroke or transient ischaemic episode
- with peripheral arterial disease

Where there are drug interactions or simvastatin 40mg is contraindicated, a lower dose or alternative preparation may be chosen.

A target for total cholesterol or LDL cholesterol is not recommended for people with established CVD who are treated with a statin. Statins should be up-titrated if the patient does not reach a total cholesterol of 4 mmol/l or LDL cholesterol 2 mmol/l on
the initial dose. This decision should be made after considering the benefits and risks of treatment and informed patient preferences.

Clinical judgment should be used for people who have comorbidities that may make such increases in treatment inappropriate, or for people receiving multiple drug therapy that may increase the risk of adverse reactions.

The criteria the GDG used to select these key priorities for implementation included whether a recommendation is likely to:

- have a high **impact** on patients’ outcomes, in particular mortality and morbidity
- have a **high impact** on reducing variation in the treatment offered to patients
- lead to a **more efficient** use of NHS resources
- enable patients to **reach important points in the care pathway more rapidly**.
2 Introduction

2.1 Background (epidemiology)

Cardiovascular disease (CVD), comprising coronary heart disease (CHD) and stroke is the main cause of death in the England and Wales. In 2005 more than one in three people died from CVD, accounting for 124 000 deaths; 39 000 of those who died were aged under 75 years (Annual update 2005 mortality statistics cause. England and Wales. 2007;33: 89-93. Health Statistics Quarterly).

For every one fatality, there are at least two people who have a major non-fatal vascular event. There are over 3 million people living with coronary heart disease or stroke. There are a further 4 million men and 1 million women who should consider treatment options because they have a one in five chance of a major CVD event in the next ten years. The inclusion of people with diabetes would further add to that total. (British Heart Foundation statistics website http://www.heartstats.org/homepage.asp).

This epidemic has been socially generated by smoking, diets high in saturated fats and salt and a sedentary lifestyle. The epidemic peaked in the 1970s and 1980s and death rates have halved since then. Despite this reduction CVD remains the leading cause of death, an increasing cause of morbidity and a major cause of disability and ill-health. The UK CVD death rates continue to exceed those of its European neighbours.

Age is the prime determining factor for cardiovascular disease. CVD is strongly associated with low income and social deprivation, with the North-South divide (both within the UK and Europe as a whole) and with men who have South Asian ethnicity, who are more likely to develop CVD at a younger age. However, lifetime burden is greater in women because of their longevity and the increased risk of stroke over the age of 75 years (Seshadri, S. et al 2006).

It is estimated that 60% of the CVD mortality decline in the UK during the 1980s and 1990s was attributable to reductions in major risk factors, principally smoking.
Treatment of individuals, including secondary prevention, accounts for the remaining 40% of the decline in mortality (Unal, B., Critchley, J. A., Capewell, S. 2004).

In spite of evidence that mortality from CVD is falling, morbidity appears to be rising. CVD has significant cost implications and was estimated to cost the NHS £14 750 million in 2003 and the economy around £30 billion a year.

Smoking, blood pressure and cholesterol account for 80% of premature coronary heart disease (Emberson, J. R. et al 2003).

CVD is a rare cause of death in the absence of these factors. Blood cholesterol has a linear relationship to the relative risk of CHD and is a key modifiable risk factor. It is estimated that over 50% of CVD in developed countries is due to blood cholesterol levels in excess of 3.8 mmol/l. Blood cholesterol can be reduced by drugs, physical activity and dietary change. A multifactorial approach yields most benefit because the effect of either increasing or reducing several risk factors is multiplicative.

2.2 Management

Strategies for prevention of CVD are threefold. First and most important are interventions to reduce the prevalence of CVD risk factors in the general population. Smoking cessation combined with changes in mean blood pressure and cholesterol through national reductions in salt intake, saturated fat consumption and increases in physical activity are fundamental to the national strategy for improvement.

Second, priority for interventions in people at high risk of developing CVD, focusing health service resources on those at greatest risk with most to gain. This latter strategy, largely based in primary care, includes smoking cessation and the identification and assessment of those at high risk with appropriate advice on diet, physical activity and treatment for high blood pressure and lipid modification. The NSF for CHD in England and Wales advocates both approaches and prioritises people with a 10-year risk of CHD of 30% or more for intervention. This is equivalent to a CVD risk of 40% and identifies around 15% of the adult population for treatment.
Third, secondary prevention for people with established cardiovascular disease involves modification of lipids. Risk factors remain at unacceptably high levels and can be further improved with advice, support and treatment, including higher intensity statins (Capewell, S. et al., 2006).

Trial evidence confirms statins reduce CVD events by around 23% and total mortality by 12% irrespective of baseline risk (Baigent, C. et al., 2005). People at highest risk after acute myocardial infarction will have greater absolute benefit than people at lower risk who have not yet had an event. The absolute benefits and cost-effectiveness of treatment depend upon the baseline risk. Statins are highly cost-effective for secondary prevention and are cost-effective for primary prevention above a 10-year CVD risk of 20%.

Although there have been major improvements in the use of statins for secondary prevention there is still substantial variation in their use by clinicians. Wider and improved use of statins would have a major public health impact. There is a need for professional guidance to clarify areas of uncertainty and set out up-to-date evidence to improve practice.

Adherence to treatment is poor even among those who have experienced a CVD event; fewer than half are taking their statins 2 years after starting them. For primary prevention, convincing people who feel well that they need lifestyle change or lifelong drug treatment requires high quality information and communication. It also requires administrative systems for follow-up and continuing support. The NICE technology appraisal, ‘Statins for the prevention of cardiovascular events’ (TA 94, 2007) recommends that the current National Service Framework threshold for statin treatment be reduced by half, to a 10-year CVD risk of 20%. This is a formidable task involving about half of men over 50 years and 20% of women over 65 years in assessment, advice and treatment decisions. It is important that such a programme reduces social inequity by age, sex, ethnicity and deprivation. Programmes must be simple, replicable, accessible for all population groups and effective. In secondary care more comprehensive and intense treatment with statins will also yield important benefits.
The use of statins has major cost implications and the prescribing of lipid-regulating drugs increased steeply from £93 million in 1996 to £600 million in 2004. If implemented in full such a programme will have a major impact on public health, on primary care workload and on health service costs and resources.

2.3 Aim of the guideline
Clinical guidelines are defined as ‘systematically developed statements to assist practitioner and patient decisions about appropriate healthcare for specific clinical circumstances’ (Committee to Advise the Public Health Service on Clinical Practice Guidelines and Institute of Medicine, 1990).

This guideline gives recommendations to clinicians and others about lifestyle modification, drug therapy, patient information and the communication of patient risk assessment and information surrounding lipid modification for primary and secondary prevention of CVD.

2.4 How the guideline is set out
The recommendations for all the topics in each clinical chapter are listed at the start of the chapter. Both the evidence statements and narratives of the research studies on which our recommendations are based are found within each topic section. The evidence statements precede the narrative for each topic. The evidence extraction reports that describe the studies reviewed are found in Appendices D and E.

2.5 Scope
The guideline was developed in accordance with a scope given by NICE. The scope set the remit of the guideline and specified those aspects of lipid modification to be included and excluded. The scope was published in August 2005 and is reproduced in Appendix B.

2.5.1 Who the guideline is intended for
This guideline is of relevance to those who work in or use the National Health Service (NHS) in England and Wales. This includes:
• healthcare professionals who work within the primary, community, community pharmacy and hospital outpatient settings. The principles will also apply in secondary care.

• those with responsibilities for commissioning and planning health services such as primary care trust commissioners, Welsh Assembly government officers

• public health and trust managers

• people (aged 18 years and older) with CVD or without established CVD but who are at high risk of developing CVD due to a combination of cardiovascular risk factors including raised blood pressure and hypertension, and/or who are overweight or obese.

2.5.2 Areas outside the remit of the guideline

The guideline does not cover people:

a) with familial hypercholesterolaemia and familial hypertriglyceridaemia (familial lipoprotein lipase deficiency; familial apolipoprotein C-II deficiency)

b) with type 1 and type 2 diabetes

c) with familial clotting disorders and/or other defined genetic disorders that increase cardiovascular risk

d) who are at high risk of CVD or abnormalities of lipid metabolism as a result of endocrine or other secondary disease processes or as a result of drug treatment

e) with a myocardial infarction (MI) (this has been covered in the NICE guideline ‘Secondary prevention in primary and secondary care for patients following a myocardial infarction’ (CG048).

This guideline also does not cover:
a) the identification, assessment and management of people with pre-diabetes/metabolic syndrome.

b) the clinical management of conditions considered to be risk factors for CVD, including raised blood pressure/hypertension, smoking, obesity, and blood clotting abnormalities.

c) self-medication of individuals with lipid-regulating drugs, specifically use of over-the-counter drugs, including statins.

d) the clinical management of people with lipid disorders considered to merit referral to secondary care for specialist assessment and follow-up.

e) the clinical management of people with CHD (angina), stroke and peripheral arterial disease except as it relates to lipid modification in the context of secondary prevention.

2.6 Responsibility and support for guideline development

2.6.1 The National Collaborating Centre for Primary Care (NCC-PC)

The NCC-PC is a partnership of primary care professional associations and academic units, formed as collaborating centre to develop guidelines under contract to NICE, and is entirely funded by NICE. The NCC-PC is contracted to develop five guidelines at any one time, although there is some overlap at start and finish. Unlike many of the other centres that focus on a particular clinical area, the NCC-PC has a broad range of topics relevant to primary care. However, it does not develop guidelines exclusively for primary care. Each guideline may, depending on the scope, provide guidance to other health sectors in addition to primary care.

The Royal College of General Practitioners (RCGP) acts as the NCC-PC’s host organisation. The Royal Pharmaceutical Society and the Community Practitioners’ and Health Visitors’ Association are partner members with representation of other professional and lay bodies on the Board. The RCGP holds the contract with NICE for the NCC-PC. The work has been carried out on two sites in London, where the
work on this particular guideline was based, and in Leicester under contract to the
University of Leicester.

2.6.2 The Development Team

The Development Team had the responsibility for this guideline throughout its
development. It is responsible for preparing information for the Guideline
Development Group (GDG), for drafting the guideline and for responding to
consultation comments. The development team working on this guideline consisted
of the:

Guideline Lead, who is a senior member of the NCC-PC team and has overall
responsibility for the guideline.

Information Scientist, who searched the bibliographic databases for evidence to
answer the questions posed by the GDG.

Reviewer (Senior Health Services Research Fellow), with knowledge of the field,
who appraised the literature and abstracted and distilled the relevant evidence for
the GDG.

Health Economist, who reviewed the economic evidence, constructed economic
models in selected areas and assisted the GDG in considering cost effectiveness.

Project Manager, who was responsible for organising and planning the
development, for meetings and minutes and for liaising between NICE and external
bodies.

Clinical Adviser, with an academic understanding of the research in the area and its
practical implications for the healthcare service, who advised the Development Team
on searches and interpretation of the literature.

With the exception of the Clinical Adviser, all of the Development Team was based
at the NCC-PC in London. Applications were invited for the post of Clinical Adviser,
who was recruited to work on average one half-day per week on the guideline. The
members of the Development Team attended the GDG meetings and participated in
them.
For this guideline, the Clinical Adviser also took the role of Chairman for the GDG meetings.

2.6.3 The Guideline Development Group (GDG)

The Chairman was selected for the group based on his understanding of the field. The primary role of the Chairman was to facilitate the work at GDG meetings.

GDGs are working groups whose members are chosen with the aim of encompassing the range of experience and expertise needed to address the scope of the guideline. Nominations for GDG members were invited from the relevant stakeholder organisations, who were sent the draft scope of the guideline and some guidance on the expertise needed. From the nominations, two patient representatives and the healthcare professionals joined the GDG.

Nominees who were not selected for the GDG were invited to act as Expert Peer Reviewers. They were sent drafts of the guideline during the consultation periods and invited to submit comments by the same process as stakeholders.

Each member of the GDG served as an individual expert in his or her own right and not as a representative of the nominating organisation.

In accordance with guidance from NICE, all GDG members’ interests were recorded on a standard declaration form that covered consultancies, fee-paid work, shareholdings, fellowship, and support from the healthcare industry.

- Full GDG members were:

  Dr John Robson (Chair and Clinical Adviser)

  Senior Clinical Lecturer, General Practice, Institute of Community Health Sciences, Queen Mary University London

  Dr Peter Brindle

  General Practitioner, Bristol

  Dr Paramjit Gill
Co-opted GDG members, attending meetings where their expertise was required, were:
1 Professor Phillip Bath
2 Stroke Association Professor of Stroke Medicine, University of Nottingham
3 Dr Jane Skinner
4 Consultant Community Cardiologist, The Newcastle upon Tyne Hospitals NHS Foundation Trust
5 Ms Alison Mead
6 Cardiac Prevention and Rehabilitation Dietitian, Hammersmith NHS Trust and Imperial College
7 Dr Dermot Nealy
8 Consultant Chemical Pathologist and Lipidologist
9 Newcastle upon Tyne Hospitals NHS Trust, Royal Victoria Infirmary

- Members of the GDG from the NCC-PC were:
10 Dr Tim Stokes (until December 2006) Dr Norma O'Flynn (from February 2007)
11 Guideline Lead and Clinical Director, National Collaborating Centre for Primary Care
12 Dr Angela Cooper
13 Senior Health Services Research Fellow, National Collaborating Centre for Primary Care
14 Ms Nicola Browne
15 Health Services Research Associate, National Collaborating Centre for Primary Care (from August 2006)
16 Ms Rifna Mannan
17 Health Services Research Fellow, National Collaborating Centre for Primary Care (until August 2006)
2.6.4 Guideline Development Group Meetings

The GDG met at 4- to 5- week intervals for 18 months to review the evidence identified by the Development Team, to comment on its quality and relevance and to develop recommendations for clinical practice based on the available evidence. The final recommendations were agreed by the full GDG, which met following the consultation to review and agree any changes to the guideline resulting from stakeholder comments.

2.7 Care pathways

Two clinical care pathways have been designed to indicate the essential components of lipid modification for the primary and secondary prevention of CVD.
2.7.1 Primary prevention care pathway

NOTE: Boxes numbered alphabetically for identification purposes only.

A. Population: People aged 40 years or more

B. Exclude people with:
- Atherosclerosis, myocardial infarction, acute coronary syndrome, angina, stroke, transient ischaemic attack, peripheral arterial disease
- Type 1 and 2 diabetes
- Familial lipid disorders
- Clothing disorders or other conditions which increase cardiovascular risk
- Palliative care or other situations where preventive treatment for CVD may be inappropriate

C. Prioritise those at greater than 20% CVD risk for formal risk assessment
Rank prior CVD risk of the general practice population over 40 years using recommended risk equation, based upon pre-existing records of risk factors or estimates if they are not recorded.

D. Discuss the consequences and benefits of cardiovascular risk assessment
Formally assess risk in those wishing to proceed

E. Self presenting

F. CVD risk assessment
- Smoking status
- Blood pressure (average 2 readings)
- Measure total and HDL cholesterol
- Calculate 10 yr CVD risk using recommended risk equation
- Modify risk where appropriate

G. Risk modifiers
- South Asian men
- Positive family history of CHD
- Risk factors at high levels (smoking, blood pressure or obesity, cholesterol)
- Social deprivation

H. Advise all patients where appropriate
- Smoking cessation
- Anti-hypertensive treatment control BP <140/90mmHg
- Diet and weight control. Physical activity
- Alcohol reduction

I. CVD risk < 20%
- Reinforce lifestyle advice

J. CVD risk 20% or more
- Present individualised risk and benefit scenarios for statin treatment using both graphical and written formats
- Fasting total cholesterol, HDL cholesterol and triglycerides,
- Fasting blood glucose, Liver function tests, Renal function
- Secondary causes of dyslipidaemia should be considered and excluded before starting lipid therapy. This should include measurement of TSH.

K. Simvastatin 40mg or Pravastatin 40mg
- A lower dose or alternative preparation may be indicated as a result of clinical contraindications.
- Repeat LFT within 6 months and at 1 year but not again unless clinically indicated
- Review risk factors annually
2.7.2 Secondary prevention care pathway

NOTE: Boxes numbered alphabetically for identification purposes only.

A. People with the following:
Myocardial infarction, acute coronary syndrome, angina, stroke, transient ischaemic episode, peripheral arterial disease or other symptomatic atherosclerotic disease

C. Advise all patients where appropriate
Smoking cessation
Diet and weight control
Physical activity
Alcohol reduction

Discuss cardiovascular risks and management options including....

Blood pressure control:
Anti-platelet agents:

CHD: Beta-blockers; ACE inhibitors

B. Assessment of risk factors
Blood pressure
BMI
Fasting total cholesterol
HDL cholesterol and triglycerides
Fasting blood glucose.
Liver function tests
Renal Function

Secondary causes of dyslipidaemia should be considered and excluded before starting lipid therapy. This should include measurement of TSH.

D. Initiate treatment with simvastatin 40mg
A lower dose or alternative preparation may be indicated as a result of clinical contraindications

E. When to increase to a high intensity statin
If a level of 4mmol/l total cholesterol OR 2 mmol/l LDL cholesterol is not achieved on the initial dose, change to a higher intensity statin.

F. Annual review
Repeat LFT within 6 months and at 1 year but not again unless clinically indicated

Review lipids and risk factors at least annually or more frequently where clinically indicated
2.8 Research recommendations

2.8.1 What is the effectiveness of plant sterols and stanols in people who are at high risk of a first cardiovascular event?

Some people at increased risk of CVD might avoid the need to use drugs to modify their cholesterol levels if they made sufficient changes to their diet. Plant sterols and stanols have been shown to reduce cholesterol levels, but it is not known whether the consumption of plant sterols as part of a low-fat diet will provide worthwhile additional benefit and whether they reduce cardiovascular events.

There is a need for trials to test both efficacy and effectiveness of plant sterols and stanols in people who are at high risk of a first cardiovascular event. Efficacy trials would test whether plant sterols or stanols change lipid profiles and reduce cardiovascular events under best possible conditions. Randomised controlled trials are needed to test the effectiveness of advising people who are at high risk of experiencing a first cardiovascular event to include food items containing plant sterols or stanols in a low fat diet. The trial should last for at least two years and should consider appropriate outcomes.

2.8.2 How is cardiovascular risk most effectively communicated to patients? What methods are best and how do these differ for particular groups such as older people or members of ethnic minority groups?

The methods (both the content and means of delivery) of risk communication should be guided by current evidence. Controlled trials should be conducted comparing the impact of different methods of risk communication and decision aids on patient comprehension, the patient experience of decision-making and actual treatment decisions taken by patients. The aim should be to generate recommendations for improvement of risk communication and patient decision making. The content should include absolute rather than relative risks; presenting numerical data in both words and numbers; and visual and graphical aids. Such studies might consider a number of delivery mechanisms.
including advice from a clinician, a trained ‘coach’, self-accessed educational
presentations via computer or DVDs, peer or lay advisers, and other
appropriate means. Trials should also investigate the preferences and views
of patients from different ethnic groups and of different ages and sex.

2.8.3 What is the impact of using clinical decision aids that
include an assessment of absolute risk to prioritise the
prescription of risk-reducing treatment for the primary
prevention of cardiovascular disease?

Risk scoring methods are recommended to help target preventive treatment at
patients who are asymptomatic, but at high risk of cardiovascular disease. As
with any health technology, risk scoring methods should be shown to
favourably influence individual patients’ health outcomes or risk factors, if they
are to be used in primary prevention strategies.

There are no studies involving risk scoring methods in general community
populations. Importantly, there is no evidence to support the use of computer-
based clinical decision support systems in the primary prevention of
cardiovascular disease.

Being offered long-term primary prevention treatment, or not, is highly
significant for individuals, and because of the large numbers of people
involved, the medical, financial, and social implications for society are
considerable. While the use of clinical decision aids incorporating CVD risk
assessment has intuitive appeal and is encouraged in guidelines, the
components of an effective decision aid and its impact on individuals remain
almost completely unknown.

Outcomes should include morbidity, individual absolute risk, adverse effects,
changes in risk behaviours such as smoking, changes in treatment, and a
qualitative assessment of the views of both the clinicians using the decision
aids and the people being prioritised to either receive preventive treatment or
not.
2.8.4 What is the clinical and cost effectiveness of incremental lipid lowering with HMG CoA reductase inhibitors (statins) and/or ezetimibe to reduce cardiovascular events (i) in people without established cardiovascular disease who are at >20% risk of cardiovascular events over 10 years (ii) in people with established cardiovascular disease?

Several studies with cardiovascular outcomes were identified within this guideline that randomised patients to specific doses of statins to assess the additional effect of higher intensity statins versus lower intensity statins. The incremental cost effectiveness (including adverse events) of these drugs either alone or in combination with other classes of drug to reduce cardiovascular events by treating to target levels of total cholesterol of either 5mol/l or 4mmos/l (or comparable LDL levels) is unknown.

2.8.5 How can cardiovascular risk be best estimated in contemporary UK populations in order to identify people at high risk (but without previous cardiovascular disease) for lipid modifying treatment?

Current risk estimation is based upon the American Framingham equations derived from a white suburban population in the 1960s and 1970s, when the CVD epidemic was at its peak. The Framingham equations overestimate risk by up to 50% in contemporary Northern European populations, particularly people living in more affluent areas. They underestimate risk in higher risk populations such as those most socially deprived. Framingham makes no allowance for family history of premature CHD or pre-existing treatment with antihypertensives.

There is an urgent need to develop equations appropriate for use in England, Wales and Northern Ireland that are at least as good if not better than the existing Framingham equations in their ability to discriminate people at high risk, that are superior in their calibration and, that include appropriate weighting for social deprivation, family history and pre-existing treatment.
2.9 Acknowledgements

We gratefully acknowledge the contributions of ...[to be inserted in final document post consultation]

2.10 Glossary

<table>
<thead>
<tr>
<th>Term</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acute coronary syndrome (ACS)</td>
<td>Severe ischaemic episode associated with chest pain</td>
</tr>
<tr>
<td>Atherosclerosis</td>
<td>A general term describing hardening, narrowing and loss of elasticity of arteries. It results from a deposition of rigid collagen in the arterial wall and also from the development of fatty plaques or atheroma on the inside of the artery wall. This increases the stiffness, decreases the elasticity of the artery wall and narrows the artery. The deposition of dietary fat as atheroma is the major factor in atherosclerosis which may be made worse by high blood pressure, smoking or other factors particularly when several factors are present at the same time. Atheromatosus plaques may then be the site of blood clots that further narrow or even close the artery with resulting loss of oxygen and damage to the affected organ.</td>
</tr>
<tr>
<td>Cardiovascular event</td>
<td>Fatal or non-fatal myocardial infarct; acute coronary syndrome; fatal or non-fatal stroke; transient ischaemic attack</td>
</tr>
<tr>
<td>Cardiovascular risk (CVD)</td>
<td>The risk of a cardiovascular event occurring</td>
</tr>
<tr>
<td>Cardiovascular risk assessment</td>
<td>Involves the use of predictive equations and the adjustment of cardiovascular risk estimates based on clinical assessment or social factors such as ethnicity, family history or social deprivation or other relevant factors.</td>
</tr>
<tr>
<td>Cardiovascular outcomes</td>
<td>One or more of the following: death from stroke or myocardial infarction; non-fatal myocardial infarction or stroke; transient ischaemic episodes; acute coronary syndrome; angina; clinical interventions such as revascularisation are also considered as outcomes in some studies.</td>
</tr>
<tr>
<td>CVD: Cardiovascular disease</td>
<td>In this document CVD refers to the combined outcome fatal and non-fatal myocardial infarction, fatal and non fatal stroke, transient ischaemic attack, angina and acute coronary syndrome.</td>
</tr>
<tr>
<td>Clinical risk stratification</td>
<td>A method of allocating patients to different levels of risk of them suffering an adverse event, based on their clinical characteristics</td>
</tr>
<tr>
<td>Cost-benefit analysis</td>
<td>A type of economic evaluation where both costs and benefits of healthcare treatment are measured in the same monetary units. If benefits exceed costs, the evaluation would recommend providing the treatment.</td>
</tr>
<tr>
<td>Cost-consequences</td>
<td>A type of economic evaluation where various health outcomes are</td>
</tr>
</tbody>
</table>
Cost-effectiveness analysis reported in addition to cost for each intervention, but there is no overall measure of health gain.

Cost-effectiveness analysis
An economic study design in which consequences of different interventions are measured using a single outcome, usually in ‘natural’ units (for example, life-years gained, deaths avoided, heart attacks avoided, cases detected). Alternative interventions are then compared in terms of cost per unit of effectiveness.

Cost-effectiveness model
An explicit mathematical framework, which is used to represent clinical decision problems and incorporate evidence from a variety of sources in order to estimate the costs and health outcomes.

Cost-minimisation analysis
An economic evaluation that finds the least costly alternative therapy after the proposed interventions has been demonstrated to be no worse than its main comparator(s) in terms of effectiveness and toxicity.

Cost-utility analysis
A form of cost-effectiveness analysis in which the units of effectiveness are quality-adjusted life-years (QALYs).

Cost-effectiveness ratio
A type of economic evaluation where both costs and benefits of healthcare treatment are measured in the same monetary units. If benefits exceed costs, the evaluation would recommend providing the treatment.

Decision analysis
A systematic way of reaching decisions, based on evidence from research. This evidence is translated into probabilities, and then into diagrams or decision trees which direct the clinician through a succession of possible scenarios, actions and outcomes.

Decision problem
A clear specification of the interventions, patient populations and outcome measures and perspective adopted in an evaluation, with an explicit justification, relating these to the decision which the analysis is to inform.

Discounting
Costs and benefits incurred today have a higher value than costs and benefits occurring in the future. Discounting health benefits reflects individual preference for benefits to be experienced in the present rather than the future. Discounting costs reflects individual preference for costs to be experienced in the future rather than the present.

Dominance
An intervention is said to be dominant if there is an alternative intervention that is both less costly and more effective.

Economic evaluation
Comparative analysis of alternative health strategies (interventions or programmes) in terms of both their costs and consequences.

Evidence statements
A summary of the evidence distilled from a review of the available clinical literature.

Evidence-based questions (EBQs)
Questions that are based on a conscientious, explicit and judicious use of current best evidence.

Extrapolation
In data analysis, predicting the value of a parameter outside the range of observed values.

Health economics
The study of the allocation of scarce resources among alternative healthcare treatments. Health economists are concerned with both increasing the average level of health in the population and improving the distribution of healthcare resources.

Health-related quality
A combination of an individual’s physical, mental and social well-being;
of life not merely the absence of disease.

Life-year A measure of health outcome that shows the number of years of remaining life expectancy.

Life-years gained Average years of life gained per person as a result of an intervention.

Median The value at the halfway mark when data are ranked in order.

Meta-regression analysis An approach for aggregating data from different clinical trials that examine the same question and report the same outcomes, and relating sources of variation in treatment effects to specific study characteristics.

Myocardial infarction (MI) Event that results in necrosis of heart muscle.

Multiple logistic regression analysis In a clinical study, an approach to examine which variables independently explain an outcome.

Number needed to harm (NNH) The number of people who need to be treated with a drug in order to harm one person in a set period of time.

Open-labelled randomised trial A study in which patients are randomised to one treatment or another, and in which the clinician or investigator is aware of which treatment arm the patient is in.

Opportunity cost The opportunity cost of investing in a healthcare intervention is the other healthcare programmes that are displaced by its introduction. This may be best measured by the health benefits that could have been achieved had the money been spent on the next best alternative healthcare intervention.

Probabilistic sensitivity analysis Probability distributions are assigned to the uncertain parameters and are incorporated into evaluation models based on decision analytical techniques (for example, Monte Carlo simulation).

Quality adjusted life-years (QALYS) An index of survival that is adjusted to account for the person's quality of life during this time. QALYS have the advantage of incorporating changes in both quantity (longevity/mortality) and quality (morbidity, psychological, functional, social and other factors) of life. Used to measure benefits in cost-utility analysis, QALYS are calculated by estimating the number of years of life gained from a treatment and weighting each year with a quality-of-life score between zero and one.

Time horizon The time span used in the NICE appraisal that reflects the period over which the main differences between interventions in health effects and use of healthcare resources are expected to be experienced, and taking into account the limitations of supportive evidence.

3 Methods

3.1 Introduction

This chapter sets out in detail the methods used to generate the recommendations for clinical practice that are presented in the subsequent chapters of this guideline. The methods are in accordance with those set out

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3.2 Developing key clinical questions

The first step in the development of the guideline was to refine the guideline scope into a series of key clinical questions (KCQs). These KCQs formed the starting point for the subsequent review and as a guide to facilitate the development of recommendations by the GDG.

The KCQs were developed by the GDG with assistance from the methodology team. The KCQs were refined into specific evidence-based questions (EBQs), specifying the interventions and outcomes to be searched for by the methodology team. These EBQs formed the basis for literature searching, appraisal and synthesis.

The total list of KCQs identified is shown in Appendix F. The methodology team and the GDG agreed that a full literature search and critical appraisal should not be undertaken for all of these KCQs in view of the time and resource limitations within the guideline development process. The methodology team, in liaison with the GDG, identified those KCQs where literature searches and critical appraisal were essential. Literature searches were not undertaken where there was already national guidance on the topic to which the guideline could cross refer. This is detailed in section 3.10 (The relationship between the guideline and other national guidance).

3.3 Literature search strategy

The purpose of searching the literature is to identify published evidence that can be used to answer the clinical questions identified by the methodology team and the GDG. The Information Scientist developed search strategies for each searchable question, with guidance from the GDG, using relevant MeSH (medical subject headings) or indexing terms, and relevant free text terms. Searches were conducted between September 2005 and August 2006. The Information Specialist agreed in advance with the Reviewer and Health Lipid modification: full guideline DRAFT (June 2007)
Economist the sources to be searched for a given question. The parameters of literature searches, including any population limits and exclusions, were detailed on pro formas developed for each question. Updated searches for each question, to identify recent evidence, were carried out in April 2007. Full details of the sources and databases searched and the search strategies are contained in Appendix F.

An initial search for published guidelines or systematic reviews was carried out on the following databases or websites: National Electronic Library for Health (NeLH) Guidelines Finder, National Guidelines Clearinghouse, Scottish Intercollegiate Guidelines Network (SIGN), Guidelines International Network (GIN), Canadian Medical Association (CMA) Infobase (Canadian guidelines), National Health and Medical Research Council (NHMRC) Clinical Practice Guidelines (Australian Guidelines), New Zealand Guidelines Group, BMJ Clinical Evidence, Cochrane Database of Systematic Reviews (CDSR), Database of Abstracts of Reviews of Effects (DARE) and Heath Technology Assessment Database (HTA).

If a recent, high quality, systematic review or guideline was identified to answer a clinical question, then in some instances no further searching was carried out.

Depending on the question, some or all of the following bibliographic databases were also searched to the latest date available: MEDLINE, EMBASE, CINAHL, CENTRAL (Cochrane Controlled Trials Register), PsycINFO, Allied & Complementary Medicine (AMED).

### 3.4 Identifying the evidence

After the search of titles and abstracts was undertaken, full papers were obtained if – based on abstract and title – they appeared relevant to the topic addressed in the GDG’s question. The highest level of evidence was sought first. Wherever appropriate, the searches for evidence for both primary and secondary cardiovascular disease prevention were conducted simultaneously, and the results of these were then scanned to address separate questions.
Where randomised controlled trials were not available, observational studies, surveys and expert formal consensus results were used. Only papers published in English were reviewed. Following a critical review of the full version of the study, articles not relevant to the subject in question were excluded. Studies that did not report on relevant outcomes were also excluded. Submitted evidence from stakeholders was included where the evidence was relevant to the GDG's clinical question and when it was either better or equivalent in quality to the research identified in the literature searches. Specialist advice was obtained from a dietitian, Alison Mead, to aid in the identification of useful terms for inclusion in searches for questions relating to lifestyle interventions.

The reasons for rejecting any paper ordered were recorded.

3.5 Critical appraisal of the evidence

The Systematic Reviewer synthesised the evidence from the papers retrieved for each question or questions into a narrative summary. These formed the basis of this guideline. Each study was critically appraised using NICE criteria for quality assessment. The information extracted from the included studies is given in Appendices D and E. Background papers, for example those used to set the clinical scene in the narrative summaries, were referenced but not extracted.

3.6 Economic analysis

The essence of economic evaluation is that it provides a balance sheet of the benefits and harms as well as the costs of each option. A well conducted economic evaluation will help to identify, measure, value and compare costs and consequences of alternative policy options. Thus, the starting point of an economic appraisal is to ensure that health services are clinically effective and cost-effective. Although NICE does not have a threshold for cost-effectiveness, interventions with a cost per quality adjusted life-year of up to £20 000 are deemed cost-effective, those between £20 000 and £30 000 may be cost-effective and those above £30 000 are unlikely to be judged cost-
effective. If a particular treatment strategy was found to yield little health gain relative to the resources used, then it could be advantageous to redeploy resources to other activities that yield greater health gain.

To assess the cost-effectiveness of the different policy questions for this guideline, a comprehensive systematic review of the economic literature relating to primary and secondary prevention of cardiovascular disease was conducted. For selected components of the guideline original cost-effectiveness analyses were performed.

**Literature review for health economics**

The following information sources were searched:


The electronic search strategies were developed in Medline and adapted for use with the other information databases. The clinical search strategy was supplemented with economic search terms. The Information Scientist carried out the searches for health economics evidence. Identified titles and abstracts from the economic searches were reviewed by a single health economist and full papers obtained as appropriate. No criteria for study design were imposed a priori. In this way the searches were not constrained to randomised controlled trials (RCTs) containing formal economic evaluations.

Papers were included if they were full/partial economic evaluations, considered patients at risk of or those who have had a cardiovascular event. Thus, patients who have had stroke, angina, peripheral artery disease, transient ischaemic stroke or myocardial infarction were considered for the secondary prevention section. Only papers written in English were considered.

The full papers were critically appraised by the health economist using a standard validated checklist (Drummond, M F, Jefferson, T O, 1996). A
general descriptive overview of the studies, their quality, and conclusions was presented and summarised in the form of a narrative review.

Cost-effectiveness modelling

Some areas were selected for further economic analysis if there was a likelihood that the recommendation made would substantially change clinical practice in the NHS and have important consequences for resource use. For this guideline three areas were chosen for further economic analysis:

- Cost-effectiveness of high intensity statins compared with lower intensity statins in patients with coronary heart disease
- Cost-effectiveness of a strategy of ‘titration threshold’ (treating to target) compared with a strategy of using a standard dose of statin in people with CVD
- Cost-effectiveness of strategies for identification of patients at high risk of CVD in primary care

Full reports for each topic are in Appendix C of the guideline. The GDG was consulted during the construction and interpretation of each model to ensure that appropriate assumptions, model structure and data sources were used. All models were constructed in accordance with the NICE reference case outlined in the ‘Guideline technical manual’ (2007).

3.7 Forming recommendations

In preparation for each meeting, the narrative and extractions for the questions being discussed were made available to the GDG one week before the scheduled GDG meeting. These documents were available on a closed intranet site and sent by post to those members who requested it.

GDG members were expected to have read the narratives and extractions before attending each meeting. The GDG discussed the evidence at the meeting and agreed evidence statements and recommendations. Any
changes were made to the electronic version of the text on a laptop and projected onto a screen until the GDG were satisfied with them.

All work from the meetings was posted on the closed intranet site following the meeting as a matter of record and for referral by the GDG members.

The recommendations and evidence statements were posted on an electronic forum. The discussion was reviewed at the next meeting and the recommendations finalised.

### 3.8 Areas without evidence and consensus methodology

The table of clinical questions in Appendix F indicates which questions were searched.

In cases where evidence was sparse, or where the question was not deemed searchable, the GDG derived the recommendations via informal consensus methods, for example in the case of Question 23: ‘How necessary is it to monitor liver function tests?’

### 3.9 Consultation

The guideline has been developed in accordance with the NICE guideline development process. This has included allowing registered stakeholders the opportunity to comment on the scope of the guideline and the drafts of the full and short versions of the guideline. In addition, the draft was reviewed by an independent Guideline Review Panel (GRP) established by NICE.

The comments made by the stakeholders, peer reviewers and the GRP were collated and presented for consideration by the GDG. All comments were considered systematically by the GDG and the project team recorded the agreed responses.
3.10 The relationship between the guideline and other national guidance

3.10.1 Related NICE guidance

It was identified that this guideline intersected with the following NICE guidelines published or in development. Cross reference was made to the following guidelines when appropriate.

Clinical guidelines:

- MI: secondary prevention in primary and secondary care for patients following a myocardial infarction CG48 (2007)
- Management of type 2 diabetes: management of blood pressure and blood lipids Guideline H (2002; Guidance currently being reviewed).
- Familial hypercholesterolaemia: identification and management (ongoing)

Technology appraisals:

- Statins for the prevention of cardiovascular events in patients at increased risk of developing cardiovascular disease or those with established cardiovascular disease TA094 (2006).
- Smoking cessation: bupropion and nicotine replacement therapy. The clinical effectiveness and cost effectiveness of bupropion (Zyban) and nicotine replacement therapy for smoking cessation TA039 (2002).
- Ezetimibe for the treatment of primary (heterozygous familial and non-familial) hypercholesterolaemia (expected date of issue: November 2007)

Public health intervention guidance
Brief interventions and referral for smoking cessation in primary care and other settings. PHI1 (2006)

3.10.2 Other national guidance

In formulating recommendations consideration was given to:

5 National Service Framework (NSF) for Coronary Heart Disease (2000).

6 JBS 2: Joint British Societies' Guidelines on Prevention of Cardiovascular Disease in Clinical Practice (2005)

Reference was made to the Food Standards Agency website (www.eatwell.gov.uk/healthydiet/) for advice on cardioprotective dietary changes.

Reference was made to the Chief Medical Officer's report 2004 a: www.dh.gov.uk for advice on physical activity.

Through review of published guidance, personal contact and commenting on guideline scope, endeavours were made to ensure that boundaries between guidance were clear and advice was consistent.
### 4 Identification and assessment of people at high risk of cardiovascular disease (CVD)

#### 4.1 Recommendations

**4.1.1 Recommendations for the identification of people requiring assessment of CVD risk**

1. **4.1.1.1** For the primary prevention of CVD in primary care, a systematic strategy should be used to identify individuals likely to be at high risk.

2. **4.1.1.2** Individuals should be prioritised for assessment based upon a prior estimate of their CVD risk. This should be calculated using the recommended risk equation utilising CVD risk factors recorded in their primary care electronic medical records or estimates where these are missing, including:
   - age
   - sex
   - smoking status
   - blood pressure
   - total cholesterol
   - HDL cholesterol.

3. **4.1.1.3** Opportunistic assessment should not be routinely used in primary care to identify CVD risk in unselected individuals.
4.1.2 Recommendations for assessment of cardiovascular risk

4.1.2.1 The assessment of CVD risk should be made using Framingham 1991 10-year risk equations (Anderson, K. M., 1991)
   a) 10-year CHD risk (CHD death, non-fatal CHD including silent MI, angina, coronary insufficiency (acute coronary syndrome)
   b) 10-year risk of fatal and non-fatal stroke including transient ischaemia
   c) CVD risk = a+b.

4.1.2.2 The following endpoints for assessment are recommended to guide treatment decisions:
   • fatal and nonfatal myocardial infarction
   • acute coronary syndrome
   • stable angina
   • stroke
   • transient ischaemic attack (TIA).

4.1.2.3 People aged over 40 years should be reviewed on an ongoing basis for assessment of cardiovascular risk dependent on their CVD risk estimation.

4.1.2.4 Formal estimation of cardiovascular risk using the Framingham 1991 equations requires the following variables:
   • age: 30 – 74 years
   • sex
- blood pressure: mean of last two systolic pressures
- total cholesterol
- HDL cholesterol
- smoking status
- left ventricular hypertrophy.
4.1.2.5 The recommended risk equations should not be used for people with the following pre-existing conditions:

- coronary heart disease/angina
- stroke/TIA
- peripheral vascular disease
- familial hypercholesterolaemia or other monogenic disorders of lipid metabolism
- diabetes.

4.1.2.6 The risk score used to inform treatment decisions, particularly if near to the threshold, should take into account other factors that:

- may predispose the person to premature CVD
- may not be included in calculated risk estimates.

These factors include the following:

- Family history
  - The estimate of cardiovascular risk should be increased by a factor of 1.5 in individuals with a first-degree relative with a history of premature coronary heart disease (onset age younger than 55 years in fathers, sons or brothers or younger than 65 years in mothers, daughters or sisters).
  - The estimated CVD risk should be increased if more than one first-degree relative is affected. In the latter case, the risk to an individual is higher than a factor of
1.5 and may be as high as a factor of 2.0 or more.

- Ethnicity
  
  - This is an important cardiovascular risk factor that should be routinely recorded.
  
  - The estimated cardiovascular risk for South Asian men should be increased by a factor of 1.4.

- Socioeconomic status

- Recent initiation of a treatment that modifies CV risk. Risk may be underestimated in people who have started treatment such as antihypertensive treatment, or with lipid lowering drugs within the past 3 years. If the risk estimate is near to the threshold, clinical judgment should be used to determine whether further treatment of risk factors should be offered.

- Other risk factors such as severe obesity (BMI > 40kg/m²) (refer to NICE Obesity guideline, No. CG43, 2006).

4.1.2.7 Cardiovascular risk may be underestimated in people taking antihypertensive or lipid lowering drugs. Clinical judgment should be used to decide on further treatment of risk factors when people are below the 20% CVD risk threshold.
4.1.3 Recommendations for lipid measurement

4.1.3.1 Both total and HDL cholesterol should be measured for the optimal estimate of cardiovascular risk using Framingham equations.

4.1.3.2 Before starting a statin, a fasting lipid sample should be obtained to record total cholesterol, LDL cholesterol, HDL cholesterol and triglycerides.

If the person’s triglyceride level is already known to be 2mmol/l or less a fasting lipid sample is not required.

4.1.3.3 The decision to offer treatment should be made as soon as practicable after full risk factor assessment unless patient choice or clinical factors indicate that treatment is not appropriate.

4.1.3.4 People in whom familial hypercholesterolaemia or other monogenic familial disorders are suspected should be considered for further investigation and/or specialist review.

4.1.3.5 People with severe hyperlipidaemias should be considered for further investigation and/or specialist review.

4.2 Identification of people requiring assessment of CVD risk

4.2.1 Introduction

In current clinical practice formal assessment of cardiovascular risk is done opportunistically. Entry into formal cardiovascular risk assessment is dependent on whether a person consults their general practitioner/general practice and or whether a risk factor such as high total cholesterol or high blood pressure is identified. This is also dependant on whether the clinician
has the opportunity or makes the clinical decision to consider other issues in
the consultation. This is therefore a two-stage process in which some initial
choice is made over who receives a formal risk assessment. This has resulted
in relatively low levels of both risk estimation and treatment of people at high
risk of CVD and may also lead to treatment of people who are not at high risk
by current criteria (Primastea, P., Poulter, N. R., 2004), (Primastea, P.,

To improve primary prevention people at high risk must be identified and
managed in the most efficient and coherent way. Half of men over 50 years
and 20% of women over 65 years have a CVD risk of 20% or more. Within
this group are people who have risks in excess of 30% or even 40%. A
systematic approach to selection requires prior stratification of risk so that
those at highest risk are reviewed first. This will result in a more effective
choice of people for inclusion and a more efficient use of staff time and health
service resources than an opportunistic approach.

This is not to say that people should never be assessed opportunistically
outside of their rank order. Primary care will always involve opportunistic
assessment initiated by either the patient or the clinician.

General practice records are now universally computerised and a high
proportion of people have recording of smoking, blood pressure and, to a
lesser extent, serum lipids. These records contain most of the information
necessary to generate a prior estimate of cardiovascular risk based on
existing data. Where data are missing they can be imputed on the basis of
age- and sex-specific values drawn from population surveys (Marshall, T.
2006).

Using the recommended CVD risk equations, a prior estimate of CVD risk
based on pre-existing information can be obtained and the practice population
can be ranked from highest to lowest risk. Starting with those at highest risk,
people can then be invited for a formal clinical assessment and risk factor
estimation based on the measurement of blood pressure, lipids and current
smoking status and taking account of other relevant factors such as family
title

title

Evidence statements for the identification of people at high
title

Economic modelling in an English primary care population
showed that in comparison to opportunistic assessment, the
most efficient strategy for identifying people at high risk of
developing CVD is one which initially prioritises individuals
based upon a prior estimate of their CVD risk using data
already held in general practitioners’ electronic medical records.

Identification of people at high risk of developing CVD

Marshall and Rouse modeled the costs and outcomes of a series of strategies
for identification of patients eligible for CVD prevention in a primary care
population (Marshall, T. and Rouse, A. 2002).

An updated analysis by Marshall was commissioned by the GDG. It is
included in full in Appendix C and summarised below.

The population was derived from the Health Survey for England 2003 and
consisted of 4,264 individuals aged 30 to 74, free from CVD and without
diabetes. Various strategies were considered for identification of patients, the
main comparisons being made between:

- Opportunistic assessment whereby patients are assessed in random
  order
- Prioritisation by age whereby older individuals are assessed first
- Prioritisation by a prior estimate of CVD risk whereby 10-year CVD risk
  is calculated for every individual based on risk factor data held in their
electronic medical records. Two scenarios were modeled for this strategy:

1. ‘Minimum’ data are used (age, gender, antihypertensive drug treatment status).

2. ‘Semi-complete’ data are used (minimum data plus smoking status and a single blood pressure measurement).

Two effectiveness measures were used as described below and figures quoted are for a budget of £30 000 to allow comparison between strategies.

The first measure is the number of patients correctly identified as eligible for treatment. Under a range of assumptions, modeling showed that a practice devoting £30 000 of resources to patient identification can identify 34% of those eligible for treatment using an opportunistic strategy, 80% prioritising by age, 82% prioritising using a prior estimate derived from ‘minimum’ data and 92% using a prior estimate derived from ‘semi-complete’ data.

The second measure is the total number of CVD events predicted to occur in patients identified as eligible for treatment: Under a range of assumptions, modeling showed that a practice devoting £30 000 of resources to patient identification can identify for treatment patients who will suffer from the following numbers of CVD events in the next 10 years (Table 1).

Table 1

<table>
<thead>
<tr>
<th>Strategy</th>
<th>Number of CVD events identified</th>
<th>Proportion of total CVD events identified</th>
</tr>
</thead>
<tbody>
<tr>
<td>Opportunistic</td>
<td>61</td>
<td>33%</td>
</tr>
<tr>
<td>Prioritise by age</td>
<td>165</td>
<td>88%</td>
</tr>
</tbody>
</table>
Another important outcome measure is that of the misclassification of low-risk patients (10 year risk < 10%) as needing treatment. Under a range of assumptions, modeling showed that a practice devoting £30 000 of resources to patient identification would misclassify 5.6% of patients using an opportunistic strategy (95% CI 3.24 to 9.27), 0.80% of patients prioritizing by age (95% CI 0.26 to 0.87), 0.63% of patients prioritising using a prior estimate derived from ‘minimum’ data (95% CI 0.17 to 1.59) and 1.53% of patients using a prior estimate derived from ‘semi-complete’ data (95% CI 0.77 to 2.72).

In summary, strategies that prioritise patients based on either their age or a prior estimate of risk derived from electronic patient medical records were found to be significantly more efficient than opportunistic case finding. A semi-complete data set identified the greatest number of people likely to experience CVD events.

4.2.4 Cost-effectiveness

There were no cost effectiveness studies found surrounding the identification of people at high risk of developing CVD. An update of Marshall and Rouse’s cost-effectiveness model was commissioned by the GDG and is reported in section 4.2.5.

4.2.5 Identification of people at high risk of developing cardiovascular disease

An update of Marshall’s model was commissioned by the GDG and is included in full in Appendix C. The update included a Markov model estimating QALY gain from lifetime treatment with statins and the costs in different age bands and CVD risk bands, using population data derived from the Health Survey for England 2003 and consisting of 4,264 individuals aged 30 to 74, free from CVD and without diabetes. Various strategies were considered for identification of patients, the main comparisons being made between:

- Opportunistic assessment whereby patients are assessed in random order.
- Prioritisation by age whereby older individuals are assessed first
- Prioritisation by a prior estimate of CVD risk whereby ten-year CVD risk is calculated for every individual based on risk factor data held in their electronic medical records

For each strategy, the effectiveness measures were the number of patients identified as eligible for treatment. The most efficient strategy will allocate people earlier; they will thus benefit from the statins. The efficient strategy will also misclassify fewer people as needing treatment.

The cost-effectiveness outcome was cost per QALY by decile for the different strategies

If all patients in this population of 4,264 were assessed, the model estimates that 652 individuals will be diagnosed as clinically eligible for treatment. Untreated, we would expect these individuals to suffer from 81 CVD events over the next 10 years. We would expect the 652 individuals diagnosed as clinically eligible for treatment to include 14 (2% of the total) individuals at low risk of CVD (less than 10% 10-year CVD risk) who had been misclassified as eligible for treatment. The screening process will identify 1% of the population aged 35-44 years as eligible while the majority 87% of the patients will be aged over 65 (see table 2).
### Table 2 Percentage eligible for treatment by CVD risk bands

<table>
<thead>
<tr>
<th>CVD risk category</th>
<th>Numbers</th>
<th>Percentages</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;10%</td>
<td>14</td>
<td>2%</td>
</tr>
<tr>
<td>10-15%</td>
<td>9</td>
<td>1%</td>
</tr>
<tr>
<td>15-20%</td>
<td>103</td>
<td>16%</td>
</tr>
<tr>
<td>20-25%</td>
<td>185</td>
<td>28%</td>
</tr>
<tr>
<td>25-30%</td>
<td>132</td>
<td>20%</td>
</tr>
<tr>
<td>30-35%</td>
<td>109</td>
<td>17%</td>
</tr>
<tr>
<td>35-40%</td>
<td>53</td>
<td>8%</td>
</tr>
<tr>
<td>40-45%</td>
<td>30</td>
<td>5%</td>
</tr>
<tr>
<td>&gt;45%</td>
<td>17</td>
<td>3%</td>
</tr>
<tr>
<td>Totals</td>
<td>652</td>
<td>100%</td>
</tr>
</tbody>
</table>
Figure 1 Proportions of patients eligible for statin treatment in different age groups by CVD risk band

We estimated the QALY gain from a Markov model per person on statin treatment broken down by age and CVD risk band. The model estimated that the younger patient will benefit from more QALYs than the elderly patients, which is expected given that QALYs are calculated using life expectancy and quality of life estimates. We then calculated the QALY gain by each screening strategy and decile. Table 3 below shows the lifetime QALY gain by age and risk band and table 4 shows the QALY gain by decile and strategy for all age groups and risk bands. 95% of the QALY gains from prior CVD assessment are realised in decile 3, which is when 30% of the practice population is screened. In contrast opportunistic screening will have 28% while age has 76% when 30% of the total practice is screened.
### Table 3 Lifetime QALY gains by age and risk band from the Markov model

<table>
<thead>
<tr>
<th>Age band</th>
<th>&lt;10%</th>
<th>10-15%</th>
<th>15-20%</th>
<th>20-25%</th>
<th>25-30%</th>
<th>30-35%</th>
<th>35-40%</th>
<th>40-45%</th>
<th>&gt;45%</th>
</tr>
</thead>
<tbody>
<tr>
<td>55-64</td>
<td>12.74</td>
<td>11.72</td>
<td>11.28</td>
<td>10.96</td>
<td>10.72</td>
<td>10.54</td>
<td>10.39</td>
<td>10.26</td>
<td>10.16</td>
</tr>
<tr>
<td>65-74</td>
<td>10.21</td>
<td>9.32</td>
<td>8.93</td>
<td>8.64</td>
<td>8.42</td>
<td>8.25</td>
<td>8.11</td>
<td>7.99</td>
<td>7.89</td>
</tr>
<tr>
<td>Over 75</td>
<td>7.51</td>
<td>6.88</td>
<td>6.50</td>
<td>6.25</td>
<td>6.06</td>
<td>5.90</td>
<td>5.77</td>
<td>5.67</td>
<td>5.58</td>
</tr>
</tbody>
</table>

### Table 4 Number of QALY gains by decile in each strategy

<table>
<thead>
<tr>
<th>Decile</th>
<th>Prior CVD</th>
<th>Opportunistic</th>
<th>Age</th>
<th>Age&gt;50then&gt;40</th>
</tr>
</thead>
<tbody>
<tr>
<td>Decile 1</td>
<td>2617</td>
<td>457</td>
<td>1515</td>
<td>991</td>
</tr>
<tr>
<td>Decile 2</td>
<td>1612</td>
<td>519</td>
<td>1138</td>
<td>899</td>
</tr>
<tr>
<td>Decile 3</td>
<td>424</td>
<td>423</td>
<td>1101</td>
<td>963</td>
</tr>
<tr>
<td>Decile 4</td>
<td>118</td>
<td>426</td>
<td>551</td>
<td>1114</td>
</tr>
<tr>
<td>Decile 5</td>
<td>43</td>
<td>467</td>
<td>385</td>
<td>647</td>
</tr>
<tr>
<td>Decile 6</td>
<td>41</td>
<td>543</td>
<td>102</td>
<td>125</td>
</tr>
<tr>
<td>Decile 7</td>
<td>40</td>
<td>506</td>
<td>101</td>
<td>140</td>
</tr>
<tr>
<td>Decile 8</td>
<td>20</td>
<td>597</td>
<td>28</td>
<td>45</td>
</tr>
<tr>
<td>Decile 9</td>
<td>89</td>
<td>555</td>
<td>62</td>
<td>46</td>
</tr>
<tr>
<td>Decile 10</td>
<td>15</td>
<td>519</td>
<td>31</td>
<td>43</td>
</tr>
</tbody>
</table>
### Table 5 Percentage of QALY gains by decile in each strategy

<table>
<thead>
<tr>
<th>Decile</th>
<th>Prior CVD</th>
<th>Opportunistic</th>
<th>Age</th>
<th>Age&gt;50 then&gt;40</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>57%</td>
<td>9%</td>
<td>38%</td>
<td>20%</td>
</tr>
<tr>
<td>2</td>
<td>31%</td>
<td>11%</td>
<td>24%</td>
<td>18%</td>
</tr>
<tr>
<td>3</td>
<td>7%</td>
<td>8%</td>
<td>20%</td>
<td>20%</td>
</tr>
<tr>
<td>4</td>
<td>2%</td>
<td>8%</td>
<td>9%</td>
<td>23%</td>
</tr>
<tr>
<td>5</td>
<td>1%</td>
<td>9%</td>
<td>5%</td>
<td>13%</td>
</tr>
<tr>
<td>6</td>
<td>0%</td>
<td>11%</td>
<td>1%</td>
<td>2%</td>
</tr>
<tr>
<td>7</td>
<td>0%</td>
<td>11%</td>
<td>1%</td>
<td>2%</td>
</tr>
<tr>
<td>8</td>
<td>0%</td>
<td>12%</td>
<td>0%</td>
<td>0%</td>
</tr>
<tr>
<td>9</td>
<td>1%</td>
<td>11%</td>
<td>1%</td>
<td>0%</td>
</tr>
<tr>
<td>10</td>
<td>0%</td>
<td>10%</td>
<td>0%</td>
<td>0%</td>
</tr>
</tbody>
</table>

### Table 6 QALY loss due to misclassification

<table>
<thead>
<tr>
<th>Decile</th>
<th>Prior CVD</th>
<th>Opportunistic</th>
<th>Age</th>
<th>Age&gt;50 then&gt;40</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>0</td>
<td>43</td>
<td>8</td>
<td>13</td>
</tr>
<tr>
<td>2</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>3</td>
<td>8</td>
<td>15</td>
<td>31</td>
<td>28</td>
</tr>
</tbody>
</table>

### Total costs

Table 7 includes lifetime costs on statin treatment from the Markov model.
The costs include costs of drugs and costs of CD events. Table 8 includes all...
the costs by strategy which includes the costs from the Markov model, plus
assessment costs and invitation costs for non-opportunistic strategies.

A strategy using prior estimate of CVD risk has the least cost in the first decile
compared with all other strategies. It also has the least costs of
misclassification since only a few people are deemed eligible for treatment
when they don’t need it (table 9).
## Table 7: Lifetime cost by age and risk band from the Markov model

<table>
<thead>
<tr>
<th>Age band</th>
<th>&lt;10%</th>
<th>10-15%</th>
<th>15-20%</th>
<th>20-25%</th>
<th>25-30%</th>
<th>30-35%</th>
<th>35-40%</th>
<th>40-45%</th>
<th>&gt;45%</th>
</tr>
</thead>
<tbody>
<tr>
<td>34-44</td>
<td>£7,780</td>
<td>£12,849</td>
<td>£14,835</td>
<td>£16,192</td>
<td>£17,165</td>
<td>£17,892</td>
<td>£18,456</td>
<td>£18,905</td>
<td>£19,273</td>
</tr>
<tr>
<td>45-54</td>
<td>£7,780</td>
<td>£12,849</td>
<td>£14,835</td>
<td>£16,192</td>
<td>£17,165</td>
<td>£17,892</td>
<td>£18,456</td>
<td>£18,905</td>
<td>£19,273</td>
</tr>
<tr>
<td>55-64</td>
<td>£6,701</td>
<td>£11,609</td>
<td>£13,707</td>
<td>£15,226</td>
<td>£16,374</td>
<td>£17,272</td>
<td>£17,993</td>
<td>£18,584</td>
<td>£19,079</td>
</tr>
<tr>
<td>65-74</td>
<td>£5,389</td>
<td>£9,625</td>
<td>£11,488</td>
<td>£12,854</td>
<td>£13,892</td>
<td>£14,706</td>
<td>£15,360</td>
<td>£15,896</td>
<td>£16,344</td>
</tr>
<tr>
<td>Over 75</td>
<td>£3,823</td>
<td>£7,140</td>
<td>£8,682</td>
<td>£9,847</td>
<td>£10,750</td>
<td>£11,469</td>
<td>£12,052</td>
<td>£12,534</td>
<td>£12,938</td>
</tr>
<tr>
<td>Totals per risk band</td>
<td>£31,473</td>
<td>£54,072</td>
<td>£63,547</td>
<td>£70,311</td>
<td>£75,346</td>
<td>£79,231</td>
<td>£82,317</td>
<td>£84,824</td>
<td>£86,907</td>
</tr>
</tbody>
</table>

## Table 8: Total cost by strategy and decile

<table>
<thead>
<tr>
<th>DECILE</th>
<th>Prior CVD</th>
<th>Opportunistic</th>
<th>Age</th>
<th>Age&gt; 50then &gt;40</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>£4,798,485</td>
<td>£4,813,024</td>
<td>£21,894,643</td>
<td>£11,418,787</td>
</tr>
<tr>
<td>2</td>
<td>£2,609,381</td>
<td>£983,892</td>
<td>£2,074,527</td>
<td>£1,649,841</td>
</tr>
<tr>
<td>3</td>
<td>£773,933</td>
<td>£804,640</td>
<td>£1,852,549</td>
<td>£1,741,600</td>
</tr>
<tr>
<td>4</td>
<td>£319,024</td>
<td>£819,757</td>
<td>£986,095</td>
<td>£2,022,785</td>
</tr>
<tr>
<td>5</td>
<td>£223,575</td>
<td>£865,016</td>
<td>£708,822</td>
<td>£1,232,454</td>
</tr>
<tr>
<td>6</td>
<td>£203,999</td>
<td>£966,576</td>
<td>£306,052</td>
<td>£323,994</td>
</tr>
</tbody>
</table>

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<table>
<thead>
<tr>
<th></th>
<th>Prior CVD</th>
<th>Opportunistic</th>
<th>Age &gt; 50 then &gt;40</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>£430</td>
<td>£201,838</td>
<td>£46,898</td>
</tr>
<tr>
<td>2</td>
<td>£5,586</td>
<td>£87,887</td>
<td>£31,797</td>
</tr>
<tr>
<td>3</td>
<td>£29,175</td>
<td>£96,341</td>
<td>£71,168</td>
</tr>
</tbody>
</table>

**Note:**
- **Figure 2 Total cost by strategy in each decile**

**Table 9 Total costs of misclassification**

<table>
<thead>
<tr>
<th>Deciles</th>
<th>Prior CVD</th>
<th>Opportunistic</th>
<th>Age &gt; 50 then &gt;40</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>£430</td>
<td>£201,838</td>
<td>£46,898</td>
</tr>
<tr>
<td>2</td>
<td>£5,586</td>
<td>£87,887</td>
<td>£31,797</td>
</tr>
<tr>
<td>3</td>
<td>£29,175</td>
<td>£96,341</td>
<td>£71,168</td>
</tr>
</tbody>
</table>
1 Cost-effectiveness

A strategy based on prior estimate CVD assessment results in fewer costs and more QALYs in decile 1 compared with other strategies; thus it dominates all its comparators. The least efficient strategy is opportunistic assessment. The second best strategy is prioritising by age alone followed by age > 50 then >40. Figure 3 shows QALYs and costs by each strategy.

7 Figure 3 Cost-effectiveness plane for the different screening strategies

The model was stable in sensitivity analysis, when the costs of personnel doing the assessment and of inviting people for assessment were included. The cost-effectiveness improved further when it was assumed patients were on both antihypertensive treatment and statins.

In conclusion, prioritising patients by prior CVD risk data held in general practice is the most cost effective way of identifying people at high risk of developing CVD. Opportunistic strategy is the least efficient way.
**Lipid measurement**

4.2.6 Introduction

HDL cholesterol is an independent predictor of cardiovascular risk, high levels being ‘protective’ and levels below 1mmol/l associated with increased risk. The inclusion of the total/ HDL cholesterol ratio as a component of risk estimation has a substantial impact compared with the use of total cholesterol alone. A person with a total cholesterol of 5.2mmol/l and an HDL cholesterol of 0.7mmol/l has a ratio of 7.4 which confers a greater CVD risk than someone with a total cholesterol of 8mmol/l and an HDL cholesterol of 1.6mmol/l who has a ratio of 5.0. The ratio of total cholesterol/HDL cholesterol has been shown to be the optimal predictor of CVD risk when incorporated in multiple risk factor equations (Grover, S. A., Coupal, L., and Hu, X. P. 1995).

The GDG also considered the number of pre-treatment readings, the utility of a fasting lipid profile prior to treatment and the time in which treatment should usually be initiated. Concern has been expressed about the lack of laboratory standardisation for lipid measurement.

4.3 Assessment of cardiovascular risk

4.3.1 Introduction

Estimates of CVD risk derived from equations are not an exact science but are better than clinical judgment alone for the estimation of CVD risk. A number of risk assessment equations are available that estimate cardiovascular risk in individuals. They have been derived from studies of individuals who have been followed up often for substantial lengths of time. They predict risk best in the type of population from which they were derived. Equations derived from North American populations from the 1960s to the 1980s when coronary heart disease was at its peak overestimate risk in contemporary European populations by around twofold in Southern European populations and by 50% or more in Northern European populations including the UK. Conversely, such equations may unde-estimate risk in populations.
1. such as people with diabetes, South Asian men or the most socially deprived
2. who are at higher than average risk.
### 4.3.2 Evidence statements for assessment of cardiovascular risk

#### 4.3.2.1 Different risk assessment methods exist. Framingham derived methods dominate and are likely to be as good if not better than any other model used for cardiovascular risk estimation. The most widely used and researched are derived from the Framingham cohort.

In representative populations, recognised Framingham-based methods offer reasonable discrimination between high- and low-risk individuals but tend to overestimate the absolute risk of CVD in lower risk populations and underestimate risk in high-risk populations. There has been concern that estimates derived from North American populations dating back 30 years may not accurately estimate risk in contemporary European populations when coronary heart disease mortality has fallen by more than half during this period. Overall the Framingham risk equation is likely to over estimate risk in the current UK population, more so in Southern England than Northern England or Scotland.

Framingham-based methods may underestimate risk in people at high risk such as people with diabetes, a strong family history of premature CVD, certain ethnic groups and those from relatively socio-economically deprived backgrounds. They may also underestimate risk in people with extreme risk factors or other clinical risks not included in the model.

Framingham risk estimates do not include socio-economic factors. Nor do they usually incorporate family history of premature CVD or ethnicity.

There are no consistent differences in the generalisability of one Framingham model over another.
The following endpoints have been used by the statin technology appraisal report to establish treatment thresholds: fatal and non-fatal myocardial infarction, acute coronary syndrome, stable angina, stroke, and transient ischaemic attacks. (NICE technology appraisal 94, ‘Statins for the prevention of cardiovascular events’ 2007).

When used in conjunction with the Framingham estimates, those defined by the NICE Technology Appraisal are the most appropriate. When considering management strategies based on other risk equations, endpoints such as revascularisation, peripheral vascular disease and other disease processes associated with atherosclerosis may also be relevant.

Framingham based risk scoring methods do not accurately estimate risks in some groups of people.

Several risk factors have not been included in the Framingham risk equations and some adjustment of this risk estimate may be required to more accurately represent an individual’s absolute risk:

- Family history of a premature event from CVD: first-degree male relatives under the age of 55 years and first-degree female relatives under the age of 65 years
- Ethnic group
- Socio-economic status
- People already on treatment that modifies CV risk
- Extremes of risk factors, for example people who have a body mass index over 40kg/m².

There are differences in cardiovascular risk between black and
minority ethnic groups and the white population in England and Wales.

For men, the risk of CVD was higher in South Asian ethnic groups (with some subgroup heterogeneity) than for men in the white population.

For men there is no robust evidence for a difference in the risks of CVD other than that between South Asian ethnic groups and the general population.

For women there is no robust evidence for a difference in the risks of CVD between South Asian ethnic groups (with considerable subgroup heterogeneity) and the general population.

<table>
<thead>
<tr>
<th>4.3.2.5</th>
<th>There is increased risk of CVD in people with a family history of premature CVD.</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Cohort studies have shown a consistent association between having a positive family history of CVD and an increased risk of developing CVD. This risk remains even when adjusted for age, social class, body mass index, systolic blood pressure, blood lipids (cholesterol, triglycerides), fasting glucose and smoking status. The exact relative risk varies according to sex and nature of relationship between the individual with premature CVD and the index case.</td>
</tr>
<tr>
<td></td>
<td>The younger the age at which the family event occurred and the greater the number of family members involved, the greater the risk.</td>
</tr>
</tbody>
</table>

| 4.3.2.6 | Cardiovascular risk is closely associated with socio-economic status. Framingham equations do not include socio-economic status and underestimate risk in people who are relatively |
socially deprived. The use of equations that do not include a measure of socio-economic status may exacerbate inequalities in CVD.

**4.3.2.7** Little evidence was found supporting or refuting the assumption that cardiovascular risk assessment by clinicians improves health outcomes. The interventions showed no improvement in predicted absolute cardiovascular risk or in declared primary outcomes.

A study in hypertensive patients has shown a small reduction in systolic blood pressure associated with the use of a risk chart but not when used in conjunction with a computer based clinical decision support system.

Another study has shown very low uptake of risk-scoring methods by clinicians that would have obscured any beneficial effect on blood pressure by the intervention.

The accuracy of use of chart based systems has been questioned.

Current evidence is an insufficient basis on which to judge the effectiveness of CVD risk estimation as a method of improving health outcomes.

### 4.3.3 Methods for multiple risk factor assessment to estimate absolute cardiovascular risk in people who are at risk of CVD

A recent systematic review (Beswick, A. D. et al 2005) (Appendix J) was used as the evidence source. This review compared the accuracy of risk scoring methods such as charts and tables compared with full prediction models, namely, the Framingham-Anderson model of 1991 (Anderson, K. M.)
Eleven derived risk charts, tables and nomograms were identified comparing risk calculations with the original Framingham-Anderson prediction model (1991).

The tools identified were as follows:

- Sheffield tables (2 versions),
- Joint British Societies (JBS) charts (2 versions),
- Joint European Societies (JBS) charts (2 versions),
- Canadian nomograms,
- New Zealand charts (3 versions) and the World Health Organization and the International Society for Hypertension (WHO-ISH) chart.

It was found that the early versions of the Sheffield Tables and the Joint European Societies charts had poor sensitivity as they did not include individual values for HDL cholesterol in the risk calculation. More recent Sheffield tables and Joint British Society charts show reasonable sensitivity and specificity compared with the full Framingham Anderson model. The 1997 Canadian nomograms included HDL cholesterol in their risk calculation however they were very poor at identifying patients at high levels of risk. The WHO-ISH 1999 table suffers from generalisation of the Framingham-Anderson model with risk factor counting substituting for continuous clinical variables. The New Zealand charts have only moderate sensitivity and specificity and provide assessment of CVD risk. The most recent Joint British Society charts estimate CVD risk but were not available at the time of this review.

In conclusion, the systematic review by Beswick et al (Beswick, A. D., Brindle, P., Fahey, T. et al 2005) (Appendix J) showed that comprehensive
information is required in risk tables and charts. The inclusion of HDL
cholesterol gives the most accurate estimate of cardiovascular risk.

4.3.3.1 **Endpoints used for assessment when estimating cardiovascular risk**

The choice of CVD endpoint is important as it affects the numbers of people
reaching treatment thresholds and the numbers targeted for risk reduction
treatments.

When using Framingham the endpoints recommended in this guideline are
the same as those used in the NICE Technology Appraisal 94: Statins for the
prevention of cardiovascular events (2006). The scope for this guideline
includes risk factor modification for symptomatic atherosclerotic vascular
disease including revascularisation and peripheral arterial disease and these
endpoints should be included where appropriate in other recommended risk
equations.

4.3.3.2 **Adjusting the calculated cardiovascular risk estimate by other risk factors**

A systematic review by Brindle *et al* (Brindle, P. M. *et al* 2006) reviewed the
accuracy of Framingham-based methods to estimate risk in populations other
than those in which the models were derived (external validation).

Data were extracted on the ratio of the predicted to the observed 10-year risk
of CVD and CHD from 27 studies with data from 71,727 participants. These
or Wilson (Wilson, P. W. F. *et al* 1998) risk scores (methods using the
outcomes of combined fatal and non-fatal CHD or CVD) and covered a wide
range of different population groups: Populations varied in nationality, age
range and sex, date of recruitment and outcomes studied. The groups studied
were representative samples of men and women, people with diabetes,
people with raised cholesterol, people on treatment for hypertension, patients
with no coronary heart disease determined by angiography and patients with
a family history of CVD.
For coronary heart disease, the predicted to observed ratios ranged from 0.43 in a study of people with a family history of CHD (that is, predicting a lower risk than was observed) to 2.87 in a study of women from Germany (PROCAM) (that is, predicting a much higher risk than was observed) (Hense, H. W. et al 2003). Under-prediction was observed in studies of higher risk patients such as those with diabetes, a strong family history of premature CVD, people from geographical areas with a high incidence of disease and people in socio-economically deprived groups.

For CVD, there was similar trend of increasing under-prediction with increasing risk of the population.

Over-prediction of risk occurs when Framingham equations are applied to populations with a lower baseline risk than that experienced by the Framingham cohort. Over-prediction was seen in lower and medium risk primary care and occupational populations in Germany (Hense, H. W., Schulte, H., Lowel, H. et al 2003), France and Northern Ireland (Empana, J. P. et al 2003) and a US screening cohort with a medium level of observed risk (Greenland, P. et al 2004). In the multicentre clinical trial of Bastuji-Garin et al, coronary heart disease risk was overestimated and this was seen across eight Western European countries and Israel (Bastuji-Garin, S. et al 2002). Within England, Wales and Scotland, over-prediction by the Framingham equations occurred in all regions but was greater in the South and the Midlands/Wales where there was relatively lower mortality and morbidity than in Scotland and the North of England (Brindle, P. et al 2003).

This systematic review shows that the accuracy of the Framingham risk estimates cannot be assumed, and that it relates to the background risk of CVD in the population to which it is being applied. Overestimation of risk tends to occur in populations with low observed risk and underestimation in high-risk groups.
4.3.3.3 Adjustment of the cardiovascular risk score to take account of ethnicity

The rates of CVD vary between ethnic groups; however, the Framingham risk score does not take ethnicity into account as a risk factor.

Studies were identified which provide evidence for differences in risk by ethnic group in the UK and the need to adjust risk estimates to take into account ethnic origin when estimating an individual’s risk of CVD (Cappuccio, F. P. et al 2002) (Quirke, T. P. et al 2003).

The method of adjustment was considered in three papers. Bhopal et al’s (2005) paper included 6,448 men and women aged 25 to 74 years from the Newcastle Health and Lifestyle Survey. The hazard ratio adjusted for age and sex for CHD death in South Asians combined compared with Europeans was 2.23 (95% CI 1.13 to 4.38), the corresponding ratio for stroke mortality was 1.35 (95% CI 0.32 to 5.7).

A study by Aarabi and Jackson (Aarabi, M. and Jackson, P. R. 2005) used risk factor data from 4,497 individuals’ identified from the Health Surveys for England 1998, who were eligible to have their risk of a first CHD event calculated by the Framingham equation. Arabi and Jackson considered adding 10 years to the age of South Asian people as the simplest way of calculating coronary heart disease risk using paper based methods. The validity of this method, which assumes an excess risk of 1.79, is uncertain.

The study by Brindle et al (Brindle, P. et al 2006) included 3,778 men and 4,544 women aged 35 to 54 years from the Health Surveys for England 1998/99 and the Wandsworth Heart and Stroke Study, both of which are community-based surveys. The authors estimated the incidence rate from prevalence data for 7 minority ethnic groups: Indians, Pakistanis, Bangladeshis, black Caribbean, Chinese (from the Health Surveys for England 1998/99) and black Africans (from the Wandsworth Heart and Stroke Study). The incidence rate was estimated because of the lack of prospective data on British black and minority ethnic groups.
The sex-specific and age-standardised prevalence ratio for CHD and for CVD for each ethnic group compared with the general British population was obtained from the Health Surveys for England 1998/99. Separate risk estimates were developed for CHD and CVD for both men and women for each ethnic group.

Calculated age-adjusted CVD prevalence ratios for seven ethnic groups showed considerable variation. In men, the highest ratio was observed in Bangladeshis (HR 1.39, CI 0.82 to 1.96) and the lowest among Chinese (HR 0.49, CI 0.16 to 0.82); in women, the highest ratio (HR 1.33, CI 0.70 to 1.96) was in Pakistanis and the lowest (HR 0.22, CI 0 to 0.53) among Chinese.

Their model requires validation using prospective data.

In summary, there is consistent evidence to support the need for adjustment of Framingham risk estimates to take account of ethnicity in UK populations but the best method for achieving this remains uncertain. Current guidance by the Joint British Societies (JBS2) (2005) recommends multiplying the Framingham score by a correction factor of 1.4 for South Asian people; however, this does not acknowledge the difference between the sexes.

It was noted that the determination of ethnicity itself is problematic despite much debate (Gill, P. S. et al 2007). It is a multidimensional concept and embodies one or more of the following: 'shared origins or social background; shared culture and traditions that are distinctive, maintained between generations, and lead to a sense of identity and group; and a common language or religious tradition'. For pragmatic reasons the self-determined Census question on ethnic group is acceptable. South Asian is a broad category and is generally defined as people assigning themselves as Indian, Pakistani or Bangladeshi.

The GDG agreed with the data compiled by Brindle et al (Brindle, P., May, M., Gill, P. et al 2006) that indicated that a risk estimate 1.4 times that of the white population was the most appropriate weighting to use for adjustment in men of South Asian origin. There was no significant increase in risk among South Asian women and their numbers were small. Although some other...
ethnic groups had low levels of risk in comparison to white people, this was not sufficiently robust on which to base a recommendation.

4.3.3.4 Adjustment of the cardiovascular risk score to take into account family history

Three studies were found addressing the extent to which family history predicts risk. These studies are the Framingham Offspring Study by Lloyd-Jones et al (Lloyd-Jones, D. M. et al 2004) the Malmo Preventive Project (MPP) by Nilsson et al (Nilsson, P. M., Nilsson, J. A., and Berglund, G. 2004)(follow up study) and the Physicians’ Health Study (PHS) and the Women’s Health Study (WHS) by Sesso et al (Sesso, H. D. et al 2001).

The Framingham Offspring Study

Lloyd-Jones et al. (Lloyd-Jones, D. M., Nam, B. H., D'Agostino, R. B., Sr. et al 2004) carried out a study to determine whether parental CVD predicts offspring events independent of traditional risk factors. The population consisted of 2,302 men and women with a mean age of 44 years in the Framingham Offspring Study, who were free of CVD and whose parents were both in the original Framingham cohort. The authors examined the association of parental CVD with an 8-year risk of offspring CVD using pooled logistic regression.

Compared with the participants with no parental CVD, those with at least 1 parent with premature CVD (onset age < 55 years in father, < 65 years in mother) had a greater risk for events, with age-adjusted odds ratios of 2.6 (95% CI 1.7 to 4.1) for men and 2.3 (95% CI 1.3 to 4.3) for women. Multivariate adjustment resulted in odds ratios of 2.0 (95% CI 1.2 to 3.1) for men and 1.7 (95% CI 0.9 to 3.1) for women. Non-premature parental CVD and parental coronary disease were weaker predictors.

The Malmo Preventive Project (MPP)

Nilsson et al (Nilsson, P. M., Nilsson, J. A., and Berglund, G. 2004) studied the adjusted relative risk of CVD events in offspring of parents with
cardiovascular mortality before 75 years. A total of 22,444 men and 10,902 women attended a screening programme between 1974 and 1992 and were followed up through national record linkage.

There was an increased risk of CVD events (mortality and morbidity) in offspring in relation to a positive family history of parental CVD mortality before 75 years. The multivariate adjusted relative risk (RR) for father-son heritage was 1.22 (95% CI 1.02 to 1.47; \( P < 0.05 \)), for mother-son heritage, \( RR = 1.51 \) (95% CI 1.23 to 1.84, \( P < 0.001 \)), for father-daughter heritage, \( RR = 1.20 \) (95% CI 0.83 to 1.73) and for mother-daughter heritage, \( RR = 0.87 \) (95% CI 0.54 to 1.41).

Subdividing parental age of early death into age groups 50-68, 69-72 and 73-75 showed a graded association for maternal influence: \( RR = 1.82 \) (95% CI 1.35 to 1.46), \( 1.55 \) (95% CI 1.14 to 2.10) and \( 1.50 \) (95% CI 1.13 to 1.98) respectively but not for paternal influence, \( RR = 1.29 \) (95% CI 0.99 to 1.69), \( 1.08 \) (95% CI 0.81 to 1.44) and \( 1.40 \) (95% CI 1.12 to 1.76) respectively using surviving parents or mortality after 75 years as the reference group.

**The Physicians’ Health Study (PHS) and the Women’s Health Study (WHS)**

Sesso et al (Sesso, H. D., Lee, I. M., Gaziano, J. M. et al 2001) prospectively studied 22,071 men from the Physicians’ Health Study (PHS) and 39,876 women from the Women’s Health Study (WHS) with data on parental history and age at MI.

Compared with men with no parental history, those with a maternal, paternal and both maternal and paternal history of MI conferred relative risks (RRs) of CVD of 1.71, 1.40 and 1.85; among women, the respective RRs were 1.46, 1.15 and 2.05.

Sesso et al. (Sesso, H. D., Lee, I. M., Gaziano, J. M. et al 2001) also looked at the effect of parental age: For men, maternal age at MI of < 50, 50 to 59, 60 to 69, 70 to 79 and ≥ 80 years had RRs of 1.00, 1.88, 1.88, 1.67 and 1.17; for women, the RRs for maternal age at MI of < 50, 50 to 59 and ≥ 60 years...
were 2.57, 1.33 and 1.52. Paternal age at MI of < 50, 50 to 59, 60 to 69, 70 to 79 and ≥ 80 years in men had RRs OF 2.19, 1.64, 1.42 1.16 and 0.92; in women, for paternal age at MI of < 50, 50 to 59 and ≥ 60 years, the RRs were 1.63, 1.33 and 1.13.

The GDG noted the continuous distribution of risk, which tended to increase the younger the age at which the family member had an event. Increased risk was noted to be present even up to age 75 years. The number of family members was also related to risk and risk was greater where female relatives were affected. For simplicity the GDG considered that risk should be adjusted by 1.5 where there was a female first-degree relative under 65 years with coronary heart disease or a first-degree male relative under 55 years. Additional family members in this category would further increase risk.

4.3.3.5 Adjustment of the cardiovascular risk score to take into account socio-economic status

There is a widening relative gap in mortality and morbidity associated with socio-economic status. There has been a substantial reduction in CVD in the past two decades but the poorer sections of society have not improved as fast as the more affluent. In 1986/92 mortality from circulatory disease was 69% greater in people from social classes IV and V than that in people in social classes I and II and by 1997/99 this had increased to 86% (White, C., von Galen, F., and Chow, Y. H. 2003). This represents a decrease between socio-economic groups in absolute mortality difference but a widening of the relative difference. This relative inequality has been a cause for governmental concern and tackling health inequalities in CVD is a major a component of current governmental strategy (Department of Health 2003). Mortality from circulatory diseases in the most deprived category of deprivation is currently threefold higher in women and 2.7 times higher in men than in the least deprived category.

During the course of this guideline development the Scottish ASSIGN score has been published and adopted as part of SIGN guidance but at the time of writing had not been validated in an English or UK population. It was
developed in a Scottish cohort. In this cohort the Framingham score
overestimated risk overall and in each quintile of social deprivation. It
substantially underestimated the variation in risk with deprivation. The relative
risk of observed 10-year coronary risk (sexes combined) analysed across
population fifths had a steep gradient, from least to most deprived, of 1.00,
1.81, 1.98, 2.22, and 2.57. Expected risk, calculated from baseline risk factor
values and the Framingham score, had one quarter of that gradient, with
relative risks of 1.00, 1.17, 1.19, 1.28, and 1.36 (Woodward, M. et al 2007)
(Tunstall-Pedoe, H. and Woodward, M. 2005). The GDG were informed of
research which aims to develop a similar score in English, Welsh and NI
populations but which was not yet completed.

Concern has been expressed that a major programme designed to increase
treatment of those at highest risk of CVD may increase social inequalities in
health by undertreatment in the most deprived sections of society and
overtreatment in the most affluent (Brindle, P. et al 2005).

4.3.3.6 What is the most effective method of delivering tools for
risk estimation to clinicians?
A systematic review has examined methods to aid the healthcare professional
in reporting cardiovascular risk score (Beswick, A. D., Brindle, P., Fahey, T. et
al 2005) (Appendix J). Only two studies were identified; one in people with a
diagnosis of diabetes and the second in people diagnosed with hypertension.
The first study compared the documentation of the cardiovascular risk score
at the front of the patient’s notes with no documentation at the front of the
For both the intervention and the control group the physicians were given
standard information on weight, haemoglobin, microalbuminuria and
cholesterol. At 6-month follow-up, treatment with antihypertensives and lipid
lowering drugs was increased in the group with clearly identified risk scoring.
However, this was only significant in patients at greater cardiovascular risk
(> 20% 5-year risk) compared with those at lower risk (≤ 20% 5-year risk).
The second study, in people with hypertension, compared the use of the Framingham-Alderson 1991 risk calculation with an estimation of cardiovascular risk by a physician (Hanon, O. et al. 2000). The physician in the intervention group was told the estimated risk calculation, while the control group had their risk estimated by a physician using clinical judgment. At eight-week follow-up, there was no benefit for inclusion of Framingham-Alderson 1991 10-year CVD risk in the therapeutic strategy. There was no difference between the groups in change in systolic and diastolic pressure or in change in prescription of antihypertensives. Concordance between the Framingham-Alderson 1991 calculated risk and the estimated risk by the physician was 35%.

A limitation to the methodological quality of the two studies is that they did not describe the method of randomisation, blinding or power calculation (Hall, L. M., Jung, R. T., and Leese, G. P. 2003) (Hanon, O., Franconi, G., Mourad, J. J. et al. 2000).

4.3.4 Cost-effectiveness

There were no cost-effectiveness studies found surrounding the most effective method of providing tools for risk estimation to people at high risk of developing CVD.
### 4.3.5 Evidence statements for lipid measurement

#### 4.3.5.1
Both HDL cholesterol and total cholesterol form integral aspects of the Framingham equations. Management decisions should use both parameters as they are known to make independent contributions to CVD risk. Total and HDL cholesterol can be measured in non-fasting specimens.

#### 4.3.5.2
Many clinicians consider that baseline information on LDL cholesterol and triglycerides is necessary for the management of people commencing treatment. Before commencing statin treatment, a fasting lipid profile is recommended, including a baseline estimate of LDL cholesterol and triglycerides.

In order to measure LDL at present, a fasting specimen is necessary which gives triglyceride measurement. The LDL level is then calculated indirectly using the Friedwald equation. (Direct methods exist but have limited availability at present).

#### 4.3.5.3
Once an individual has had their risk factors measured and is found to be in a high-risk group for which active management is recommended, it may require several consultations and some time may be necessary for this information to be conveyed and assimilated and other clinical issues addressed. It would normally be expected that these issues would be dealt with and appropriate treatment started within 6 months of full risk factor assessment.

#### 4.3.5.4
Individuals who are identified from their history or clinical findings to be at high increased risk of premature cardiovascular disease due to familial or other genetic factors require full investigation and/or specialist review. These people will include those with familial hypercholesterolaemia or monogenic lipid disorders.
4.3.6 Measurement of lipid parameters for risk assessment

Framingham takes account of the ratio of total to HDL cholesterol in estimating risk. The ratio of the total cholesterol to HDL cholesterol is a better predictor of risk than either measure alone (Grover, S. A., Dorais, M., and Coupal, L. 2003); (Nam, B. H., Kannel, W. B., and D'Agostino, R. B. 2006).

The current mean HDL level in middle-aged men in England is 1.4mmol/l, and in women it is 1.7mmol/l.

HDL estimation is now widely available in laboratories. For clinical estimation of cardiovascular risk both total and HDL cholesterol should be measured. A non-fasting specimen is sufficient.

Where prior estimation of total or HDL cholesterol is not available, then values based on the average in Health Survey for England (2003), as above are appropriate.

4.3.6.1 Accuracy of taking one reading of lipid levels versus taking repeated readings of lipid levels

Framingham risk estimates were based on a single measurement of total and HDL cholesterol and for risk estimation a single reading is sufficient.

Variability of measurement due to physiological variation, laboratory variation and statistical variation are discussed below (Monitoring lipid levels on treatment).

4.3.6.2 Monitoring lipid levels on treatment

Measured cholesterol levels incorporate an error term based on the coefficient of variation which, from published studies, is 7.2% for total cholesterol and 7.5% for HDL cholesterol (Nazir, D. J. et al 1999). This error term results from day-to-day physiological variation, from laboratory variation or sample processing and from random variation. Laboratory variation has been a
subject of concern and in the USA a national quality standard has been
established for lipid assay (Warnick, G. R. 2000) The GDG notes that there
are concerns, particularly for HDL cholesterol, that no such standardisation
exists in the UK.

Because of this individual variation in a single lipid measurement, repeated
measurement will give greater precision. Precision increases as the inverse of
the square root of the number of measurements (Thompson, S. G. and
Pocock, S. J. 1990). A total cholesterol of 4.0 mmol/l has a standard
deviation of 0.28 and from day to day will range between plus or minus 2
standard deviations to give a 95% confidence interval of between 4.56 mmol/l
to 3.44 mmol/l. In order to ensure that an individual had a 90% chance of
having a genuine total cholesterol level below 4mmol/l would require
cholesterol to be lowered to 3.67mmol/l based on one reading, to a mean of
3.76 mmol/l based on two readings and 3.80mmol/l based on an average of 3
readings.

In routine practice clinicians find that performing serial replicate reading is not
feasible and often base monitoring on one measurement and treatment
decisions on two lipid measurements, accepting the imprecision. Where
cholesterol levels are used to monitor or guide treatment, the selection of
people for optimal treatment on the basis of a single reading is therefore
somewhat arbitrary (Westgard, J. O. and Darcy, T. 2004). Some people below
the treatment threshold on a particular day may be treated inappropriately
following a single measurement below their ‘true’ level and in others
treatment may be delayed or denied by a single reading above their ‘true’
level. One of the effects of specifying a set target level to be achieved is to
tend to select patients when their day-to-day variation yields cholesterol levels
at their highest and to include a larger number of people for additional
treatment than might be expected on the basis of their ‘true’ cholesterol level.
For these reasons, among others, (discussed in section 9.3.8) we have
avoided the use of attainment targets.
The GDG recommends the mean of at least two measurements of cholesterol where drug treatment decisions are made. For routine monitoring without treatment change, a single annual reading is sufficient.

4.3.6.3 *The need for a fasting lipid measurement before starting treatment*

There was no substantive evidence to support the view that a fasting specimen is advantageous before starting treatment. It was considered by the GDG that many clinicians view LDL cholesterol and triglycerides as an important adjunct to clinical management because they may inform diagnosis and are a baseline against which the progress and effectiveness of treatment can be judged.

Where triglycerides are already known to be 2 mmol/l or less the GDG considered that a fasting specimen could be omitted as it was considered that a fasting specimen would give no additional information that would affect management.

4.3.6.4 *Waiting time between initial assessment and further measurement of risk factors*

Many trials have used a run-in period of up to 3 months before starting treatment. In addition, the practicalities of several clinic attendances to assess and discuss risk and deal with other risk factors or clinical issues may take some time. However, the GDG felt that further delay in commencing treatment should be avoided and that most people wishing to have appropriate treatment should be started within 6 months of assessment.

4.3.6.5 *Patients with lipid disorders needing specialist assessment and management*

People in whom familial hypercholesterolaemia or other monogenic familial disorders are suspected should be considered for further investigation and/or specialist review.
People with severe hyperlipidaemias should be considered for further investigation and/or specialist review.

The management of familial lipid disorders will be the subject to the forthcoming NICE guideline: Familial hypercholesterolemia: identification and management (2008).

4.3.7 Cost-effectiveness

There were no cost effectiveness studies found surrounding the measurement of lipid parameters for risk assessment.
5 Communication of patient risk assessment and information

5.1 Recommendations

5.1.1.1 Risk assessment communication should be an open, two-way exchange of evidence-based information between the individual and the healthcare professional, with an emphasis on informed decision making.

5.1.1.2 Communication of risk assessment information should take account of the individual’s age, pre-existing medical conditions, gender, ethnic group, age, literacy, occupational circumstances and any other specific needs.

5.1.1.3 The needs of individuals who are non-English speakers or who have learning difficulties should be addressed in communicating information about risk assessment.

5.1.1.4 Information about risk assessment should be provided in formats, languages and approaches that are tailored to the individual’s need.

5.1.1.5 Healthcare professionals should use everyday, jargon-free language in communicating information on risk. If technical terms are used, these should be clearly explained.

5.1.1.6 The healthcare professional should discuss the possible options in risk assessment, including the option of declining any risk assessment.

5.1.1.7 If the person’s cardiovascular risk is considered to be at a level that merits offering appropriate interventions (including statin therapy) and they decline to take up this offer, then they should be informed...
that their cardiovascular risk level should be considered again in the future.

| 5.1.1.8 | Adequate time should be set aside during the consultation to provide information on risk assessment and for questions to be answered. Further consultation may be required. |
| 5.1.1.9 | The discussion relating to the consultation on risk assessment and the individual’s decision should be documented. |
| 5.1.1.10 | People should receive information about their absolute risk of CVD, and about the absolute risk (including benefits and adverse events) of an intervention over a 10-year period in a format that: |
| 5.1.1.11 | To facilitate reduction in cardiovascular risk, the healthcare professional should also: |

- presents individualised risk and benefit scenarios
- presents the absolute risk of events numerically
- uses appropriate graphical and written formats.

- Explore any beliefs about what determines future health that may affect attitudes to changing risk
- Find out what, if anything, people have already been told about their cardiovascular risk and how they feel about it
- Assess their readiness to adopt lifestyle changes (to diet, physical activity, smoking, and alcohol consumption), to undergo investigations and to take medication (if appropriate)
- Assess their confidence in making changes to lifestyle (diet, physical activity, smoking, and alcohol consumption)
undergoing investigations and taking medication (if appropriate)

- Inform the individual of potential future management based on current evidence and best practice
- Involve them in developing shared management plan
- Check with them that they have understood what has been discussed.

5.2 Introduction

Risk communication is defined as ‘the open, two-way exchange of information and opinion about risk, leading to better decisions about clinical management’ (Edwards, A., Elwyn, G., and Mulley, A. 2002). Discussing risk with patients in the clinical consultation has become increasingly important. Patients who are better informed and involved in decisions about their own care are more knowledgeable and also more likely to adhere to their chosen treatment plan (Gigerenzer, G. and Edwards, A. 2003) (O’Connor, A. M. et al 2003).

Patients’ values and preferences vary widely, as do their attitudes to risk. A two-way exchange of information is therefore important to explore the patient’s personal beliefs to facilitate treatment decisions.

Communication of risk is not straightforward. Clinicians need to support patients in making choices by turning raw data into information that can be used to aid discussion of risk. Decisions aids are one way of facilitating this process. Decision aids are systematically developed tools to aid patients to understand and participate in medical decisions. Decision aids often include visual representations of risk information and relate this information to more familiar risks. They can be in the form of booklets, DVDs, interactive computer programmes, tapes or web-based products. There is, however, very little evidence of the effectiveness of these aids in communicating risk in patients at high cardiovascular risk.
5.3 **Evidence statements – communication of risk assessment and information**

| 5.3.1.1 | There is limited evidence of the effectiveness of different methods of communicating risk of CVD to patients. |
| 5.3.1.2 | One small randomised controlled trial piloting a computerised decision aid has suggested that an individually tailored decision aid about coronary heart disease prevention may facilitate an individual’s discussion of risks with their healthcare professional, and also may facilitate risk reduction management plans. |
| 5.3.1.3 | A systematic review of the use of decision aids in people facing health treatment or screening decisions has shown that compared with usual care, the use of decision aids:  
  - increase knowledge  
  - increase the perceived probabilities of outcome (a measure of realistic expectation)  
  - lower decisional conflict relating to feeling informed  
  - increase the proportion of people active in decision making  
  - reduce the proportion of people who remain undecided concerning their treatment options. |
| 5.3.1.4 | Descriptive studies suggest that:  
  - Numerical presentation of risk should present absolute risk of events rather than relative risk of events. Where absolute risks of events are unavailable, relative risk of events may be presented.  
  - Graphical presentation of risk may aid in the communication of risk. |
5.3.2 Clinical effectiveness of methods of communicating risk assessment to individuals at high risk of cardiovascular disease (CVD)

The use of decision aids in people facing health treatment or screening decisions has been examined in a systematic review (O'Connor, A. M., Stacey, D., Entwistle, V. et al 2003). The review had two aims: firstly to document an inventory of decision aids focused on healthcare options and secondly to review randomised controlled trials of decision aids for people contemplating healthcare decisions. The systematic review also examined studies that compared simpler decision aids with more detailed decision aids.

The systematic review identified over 200 decision aids, of which 131 were available for review. Most of these were intended to be used as a preparation for counselling about an important decision. Ninety-four were web-based, 14 were paper based, 12 were videos, 8 were audio-guided print resources, 2 were CD-ROMS and 1 was web-based with a workbook. Analysis of the quality of these aids found that the majority included potential harms and benefits, update policy, description of the development process, credentials of the developers, reference to relevant literature and were free of perceived conflict of interest. However, few decision aids contained a description of the level of uncertainty regarding the evidence, and few had been validated (O'Connor, A. M., Stacey, D., Entwistle, V. et al 2003).

Thirty of the decision aids that were identified in the inventory were assessed in 34 randomised controlled trials. The majority of these studies evaluated decision aids for people considering cancer screening, cancer therapy, and genetic testing or hormone replacement therapy. Examples of the type of decision aid that were compared with usual care are as follows: an audiotape and a booklet, a pamphlet alone, a pamphlet plus a discussion with a healthcare professional, a series of 8 pamphlet decision aids, an interactive video, and a video plus a booklet (O'Connor, A. M., Stacey, D., Entwistle, V. et al 2003). No randomised controlled trials were identified that examined decision aids in the communication of cardiovascular risk in people at high risk of developing CVD.
To determine whether the decision aids achieved their objectives a range of positive and negative effects on the process of decision making, and on the outcomes of decisions were evaluated. Although the decision aids focused on diverse clinical decisions, many had similar objectives. The outcomes were specified in advance of the review and included: knowledge, realistic expectations, decisional conflict relating to feeling informed, the proportion of people active in decision making, the proportion of people who remain undecided concerning their treatment options and choice, satisfaction with the decision aids, anxiety, and health outcomes following use of the decision aids (O’Connor, A. M., Stacey, D., Entwistle, V. et al 2003).

The studies’ knowledge tests were based on information contained in the decision aid, thereby establishing content validity. The authors of the systematic review transformed the proportion of accurate responses to a percentage scale ranging from 0% (no correct responses) to 100% (perfectly accurate responses). Perceived outcome probabilities (a measure of a measure of realistic expectation) were classified according to the percentage of individuals whose judgments corresponded to the scientific evidence about the chances of an outcome for similar people. Decisional conflict was assessed using the previously validated Decisional Conflict Scale (O’Connor, A. M. 1995). The scale measures the constructs of uncertainty and factors contributing to uncertainty (such as feeling uninformed, unclear about values, and unsupported in decision making). The scores were standardised to range from zero (no decisional conflict) to 100 points (extreme decisional conflict). Scores of 25 or lower are associated with follow-through with decisions, whereas scores that exceed 38 are associated with delay in decision making. When decision aids are compared to usual care, a negative score indicates a reduction in decisional conflict, which is in favour of the decision aid (O’Connor, A. M., Stacey, D., Entwistle, V. et al 2003).

Compared with usual care, the use of decision aids was found to increase knowledge in all of the included studies. The gains ranged from 9 to 30 percentage points and the weighted mean difference (WMD) was 19 out of 100 (95% CI 13 to 24), Decision aids increased the perceived probabilities of
outcome which was a measure of realistic expectation (RR 1.4, 95% CI 1.1 to 1.9). Decisional aids decreased decisional conflict in all of the included studies, and ranged from -2 to -10 out of 100 with a WMD of -9.1 out of 100 (95% CI -12 to -6). Compared with usual care, decisional aids increased the proportion of people active in decision making (RR 1.4, 95% CI 1.0 to 2.3), and reduced the proportion of people who remain undecided concerning their treatment options (RR 0.43, 95% CI 0.3 to 0.7). The authors commented that the findings were important for two reasons. Firstly, people’s level of knowledge and perception of health outcomes in the usual care groups appeared insufficient for informed decision making. Secondly, people’s healthcare treatment choice often changed once their knowledge and realistic expectation scores improved. Overall, these findings indicate that ‘usual care’ may be inadequate when people are facing complex value-laden decisions. These findings also suggest that people need to comprehend the options and probable outcomes to aid in their own decision making. Decision aids also may help people to communicate to their clinicians the personal value they place on the benefits versus the harms (O’Connor, A. M., Stacey, D., Entwistle, V. et al 2003).

Compared with usual care, the use of decision aids did not generally increase satisfaction with decision making, nor did their use reduce anxiety. Decision aids also did not have a consistent effect on general health outcomes. The authors noted that measurement of satisfaction is liable to insensitivity because it is more likely to be linked to the relationship of an individual with the clinician than with the decision aid. Also, satisfaction with usual care may already be high. Anxiety as an outcome measure was deemed inappropriate by the author because more effective decision strategies are associated with a moderate increase in anxiety. The predominately null effect of decision aids for health outcomes suggest that rates of actual choices can vary without affecting quality of life. However, the author suggested that in future studies it may be more appropriate to link the measurement of health outcomes to prior patient choices to provide a more accurate determination of the effect of decision aids because this was not done in the trials identified (O’Connor, A. M., Stacey, D., Entwistle, V. et al 2003).
In summary, compared with usual care strategies, the systematic review found that decision aids consistently improved an individual’s involvement in decision making. The review had a number of limitations in that there was variability in the decision contexts, variability in the design of the decision aids (content, format, and use), and in the type of comparison. The choice of the decision aid will depend upon the needs of the individual (for example literacy, motivation), the nature of the intervention to be explained and considered, and also upon the expectations of clinicians (O'Connor, A. M., Stacey, D., Entwistle, V. et al 2003).

For the comparison of simpler decision aids and more detailed decision aids the majority of the included studies had defined the simpler decision aid as pamphlets. Examples of the more detailed decision aids included an audiotape booklet, an audiotape booklet with values clarification, an interactive DVD, a pamphlet plus a video plus a decision tree, and a lecture plus a personal decision exercise (O'Connor, A. M., Stacey, D., Entwistle, V. et al 2003).

Compared with simpler decision aids, the use of more detailed decision aids were found to marginally improve knowledge (4 out of 100 (WMD), 95% CI 3 to 6) and more realistic expectations (RR 1.5, 95% CI 1.3 to 1.7). Detailed decision aids appeared to do no better than comparisons in affecting satisfaction with decision making, anxiety, and health outcomes. There was a variable effect of detailed decision aids on which healthcare option were selected (O'Connor, A. M., Stacey, D., Entwistle, V. et al 2003).

The authors stated that the small differences in knowledge scores between detailed and simpler versions of decision aids are likely due to the overlapping information presented in the two interventions. In contrast, the effects remained large for expectation measures and for agreement between values and choice. These observations may occur because the detailed interventions, in contrast to the simpler versions, generally contained probabilistic information about outcomes as well as explicit values clarification exercises. The authors also noted that the effect of providing different components of decision support within decision aids was not examined due to
lack of available data. The issue of what to include in a decision aid remains unresolved. There is a need to establish the ‘essential ingredients’ in decision aids and to identify the people who are most likely to benefit from detailed versions (O’Connor, A. M., Stacey, D., Entwistle, V. et al 2003).


The first used a cluster randomised controlled trial design with 614 patients from 27 practices in Avon. Three different methods of delivering risk factor scoring systems to clinicians were assessed: a computerised clinical decision support system (CDSS) plus cardiovascular risk chart; cardiovascular risk chart alone; or usual care (Montgomery, A. A., Fahey, T., Peters, T. J. et al 2000).

No differences were found between the CDSS plus chart group and the usual care group in terms of change in 5 year risk, change in systolic and diastolic blood pressure and odds ratios for taking 2 or 3 or more classes of drugs compared with 0 or 1. The chart-only group did have significantly lower systolic blood pressure (at 6 months) and were more likely to be prescribed cardiovascular drugs (at 12 months) compared with the usual care group. People with 5-year CVD risk > 20% were more likely to reduce their risk in the chart or computer group than in usual care. The extent to which each group adopted the use of CDSS or charts is not clear. The authors of the study suggested that the CDSS may confuse or distract the healthcare professional in their use of the chart (Montgomery, A. A., Fahey, T., Peters, T. J. et al 2000).

The second study used a cluster randomised controlled trial design with GPs from 17 Norwegian health centres either being offered CDSS or practise usual care. They found no clinically significant difference in blood pressure or
total cholesterol between the two groups at the end of the follow-up period of
21 months (Hetlevik, I., Holmen, J., and Kruger, O. 1999) (Hetlevik, I.,
Holmen, J., Kruger, O. et al 1998).

Regarding the quality of the studies, both used cluster randomisation and
participants were not blinded to their group. In addition, the first reported
losses of 14% at 12 months (Montgomery, A. A., Fahey, T., Peters, T. J. et al
2000). The second study did not conduct a power calculation or report
confidence intervals (Hetlevik, I., Holmen, J., and Kruger, O. 1999) (Hetlevik,
I., Holmen, J., Kruger, O. et al 1998).

Regarding the effectiveness of CDSS, one study showed no clinically
significant differences versus usual care but did note that despite an average
of 1.5 hours of training, uptake of CDSS in the intervention group was only
12% (Hetlevik, I., Holmen, J., and Kruger, O. 1999) (Hetlevik, I., Holmen, J.,
Kruger, O. et al 1998). The other study showed a negative effect on systolic
blood pressure when CDSS was added to a risk-chart and a greater reduction
in risk in people at high risk. No data were available on the uptake rate
(Montgomery, A. A., Fahey, T., Peters, T. J. et al 2000). It has been
suggested that the inclusion of clinicians in the design of decision aids may
improve their use (Brindle, P. M., Beswick, A. D., Fahey, T. et al 2006) and
also that paper-based cardiovascular risk tables are inaccurately used

In summary, these two studies showed limited or no difference between
groups advised to use CDSS and those providing usual care except in people
at highest risk. One study indicated uptake of CDSS was very low (Hetlevik, I.,
Holmen, J., and Kruger, O. 1999) (Hetlevik, I., Holmen, J., Kruger, O. et al
1998).

A pilot randomised trial has assessed the impact of a decision aid about heart
disease prevention in adults with no previous history of heart disease
(Sheridan, S., Pignone, M., and Mulrow, C. 2003). This was a small study; 75
people were enrolled and of these, 43% had a 10-year CVD risk of 0-5%, 25%
a risk of 6-10%, 24% a risk of 11-20% and 5% a risk of > 20%. The
intervention group were given the computerised decision aid ‘Heart to Heart’ (version 1). This calculates an individual’s global risk of CVD events in the next 10 years by combining information on an individual’s age, sex, blood pressure, total and HDL-cholesterol, smoking status, diabetes, and left ventricular hypertrophy status using a continuous Framingham equation. ‘Heart to Heart’ provides individualised information about an individual’s global CVD risk, personal risk factors, the benefits and risks of CVD risk reducing therapies (e.g. hypertension therapy, lipid lowering treatment, aspirin), and the risk reductions achievable after one or more therapeutic interventions. ‘Heart to Heart’ also encourages the individual to choose therapies that are acceptable feasible for long-term CVD risk reduction. In addition, the tool encourages the adoption of a good diet and exercise. The control group received only a list of their CVD risk factors that they could present at the clinical consultation. Forty-one people received the decision aid, and 34 people received the usual care.

Self-reported data were collected at four points in a single study consultation: during initial eligibility assessment, at baseline, after navigation of the study aid (intervention group only), and after the regularly scheduled provider visit. The main effect of the decision aid on decision making was assessed by the proportion of participants who reported discussing their CVD risk with their clinician, and by the proportion of participants who had a specific plan for CVD risk reduction at the post-visit survey. Within-group effects of the decision aid were assessed using pre-post comparisons of an individual’s perception that CVD prevention requires a decision, and the individual’s desired participation in decision making. In unadjusted analysis, the decision aid increased the proportion of participants who discussed CVD risk reduction with their clinician (absolute difference 16%, 95% CI -4% to 37%) and increased the proportion who had a specific plan to reduce their risk from 24% to 37% (absolute difference 13%, 95% CI -7% to +34%). The authors stated that there were too few participants in the trial to perform adjusted analysis. In pre-post testing analysis, the decision aid appeared to increase the proportion of people with plans to intervene on their CVD risk (absolute increase ranging from 21% to
47% for planned medication use, and 5% to 16% for planned behavioural interventions) (Sheridan, S., Pignone, M., and Mulrow, C. 2003).

The authors concluded that the trial provides preliminary evidence that an individually tailored decision aid about CVD prevention may facilitate an individual’s discussion of CVD risks with their healthcare professional, and also may facilitate in CVD risk reduction management plans (Sheridan, S., Pignone, M., and Mulrow, C. 2003).

A narrative review has discussed the presentation of medical statistics to convey risks to people contemplating a healthcare decision (Gigerenzer, G. and Edwards, A. 2003). Three specific numerical representations were identified that engender confusion, namely single event probabilities, conditional probabilities, and the use of risk relative risks.

Single event probabilities describe the chance of an event occurring in percentage form, for example ‘there is a 5% chance that drug A will cause harmful side effect B’. Confusion can arise as some individuals may interpret this to mean that ‘5% of the time taking drug A will cause harmful side effect B’. The authors stated that an individual’s perception of risk will be clearer if frequency statements are used that specify a reference class. For example, conveying the risk of harmful side effect B can be expressed as ‘5 out of every 100 people will have side effect B from taking drug A’ (Gigerenzer, G. and Edwards, A. 2003). Conditional probabilities, for example the sensitivity, specificity and a positive predictive value of a screening test, are often misunderstood. Sensitivity refers to the class of people with the illness, while specificity refers to those without the illness. Again, converting the percentage probability of a positive test and the percentage probability of an individual actually having an illness is better represented in the form of frequency statements (Gigerenzer, G. and Edwards, A. 2003).

The use of relative risks can also be misleading. The numerical risk reduction value may be incorrectly linked to the intervention population, rather than the event rate in the population that does not receive the intervention. Misinterpretation of relative risks can result in perceived gross over-estimation
of the effectiveness of an intervention. This confusion can be avoided by communicating absolute risk reductions either in the form of percentages or conversion into integers (such as a 1 in 10 chance) (Gigerenzer, G. and Edwards, A. 2003).

In summary the author concluded that single event probabilities, conditional probabilities and relative risks are confusing because they make it difficult to understand what class of events a probability or percentage refers to. The use of transparent representations (such as natural frequencies and absolute risks) clarifies the reference class and should aid in perception of risk (Gigerenzer, G. and Edwards, A. 2003). It is also important to note that presentation of risk should be given with a specified time frame (Thomson, R., Edwards, A., and Grey, J. 2005).

The visual communication of risk has been extensively described by Lipkus and Hollands (Lipkus, I. M. and Hollands, J. G. 1999). Visual displays such as graphs reveal data patterns that may be undetected in numerical information, and graphs can attract and hold people’s attention because they display information in concrete, visual terms. To be useful, graphs must convey different risk characteristics such as risk magnitude, the comparison of the magnitude of two risks, cumulative risk (i.e. observing trends over time), uncertainty, and interactions into among different risk factors. A number of different graphical representations of risk have developed, but is important to note that there is little clinical trial evidence available of the effectiveness of graphs compared with numerical representation of risk. Graphs can be in the form of risk ladders (that displays a range of risk magnitudes such that increased risk is portrayed higher up in the ladder), stick and facial figures, line graphs, dots and related formats, pie charts and histograms. There is a suggestion that simpler bar charts are preferable to more complex representations of data (i.e. pie charts, crowd figures, survival curves) (Thomson, R., Edwards, A., and Grey, J. 2005). It has been suggested that the combination of graphical and numerical risk may provide the best approach. However the visual and numerical communication of risk should be
6 Lifestyle modification for the primary prevention of cardiovascular disease (CVD)

6.1 Recommendations for lifestyle

6.1.1 Cardioprotective dietary advice

6.1.1.1 People at high risk of CVD should be advised to eat a diet in which total fat intake is 30% or less of total energy intake, saturated fats are 10% or less of total energy intake, intake of dietary cholesterol is less than 300mg/day and saturated fats are replaced by increasing the intake of monounsaturated fats. Reference can be made to the Food Standards Agency website which gives further advice (www.eatwell.gov.uk/healthydiet/).

6.1.1.2 People at high risk of CVD should be advised to eat at least five portions of fruit and vegetables per day in line with national guidance for the general population. Examples of what constitutes a portion can be found on the Food Standards Agency website (www.eatwell.gov.uk/healthydiet/).

6.1.1.3 People at high risk of CVD should be advised to consume at least two portions of oily fish per week. Please see appendix G for a table of the oil content of fish. The Food Standards Agency website gives further information and advice on healthy cooking methods (www.eatwell.gov.uk/healthydiet/).

6.1.1.4 Omega 3 fatty acid supplements should not routinely be recommended for primary prevention of CVD.

6.1.2 Plant stanols and sterols recommendations

6.1.2.1 Plant sterols and stanols should not routinely be recommended for primary prevention of CVD.
### 6.1.3 Physical activity recommendations

**6.1.3.1** People at high risk of CVD should be advised to take 30 minutes of at least moderate intensity physical activity a day, at least 5 days a week, in line with national guidance for the general population (See the Chief Medical Officer’s 2004 report at: www.dh.gov.uk).

**6.1.3.2** People who are unable to perform moderate intensity exercise at least 5 days a week because of comorbidity, medical conditions or personal circumstances should be encouraged to exercise at their maximum safe capacity.

**6.1.3.3** Recommended types of activity include those that can be incorporated into everyday life such as brisk walking, using stairs and cycling (see the Chief Medical Officer’s 2004 report at www.dh.gov.uk).

**6.1.3.4** People should be advised that shorter bouts of physical activity of 10 minutes or more accumulated throughout the day are as effective as longer sessions of activity (see the Chief Medical Officer’s 2004 report at www.dh.gov.uk).

**6.1.3.5** Advice regarding physical activity should take into account the person’s needs, preferences and circumstances. Goals should be agreed and the person should be provided with written information about the benefits of activity and the local opportunities to be active. (For further information, please see NICE public health intervention guidance ‘Four commonly used methods to increase physical activity: brief interventions in primary care, exercise referral schemes, pedometers and community-based exercise programmes for walking and cycling’ PHI002, 2006).

### 6.1.4 Combined interventions (specifically diet and physical activity) recommendations
6.1.4.1 Advice on diet and physical activity should be given in line with national recommendations.

6.1.5 Weight management recommendations

6.1.5.1 People at high risk of CVD who are overweight or obese should be offered appropriate advice and support to achieve and maintain a healthy weight in line with the NICE guideline ‘Obesity: the prevention, identification, assessment and management of overweight and obesity in adults and children’, CG43, 2006.

6.1.6 Smoking cessation recommendations

6.1.6.1 All people who smoke should be advised to quit and be offered assistance from a smoking cessation service in line with NICE public health intervention guidance ‘Brief interventions and referral for smoking cessation in primary care and other settings’, PHI001 2006.

6.1.6.2 All people who smoke and who have expressed a desire to quit should be offered support and advice, and referral to an intensive support service (for example the NHS Stop Smoking Services) in line with NICE public health intervention guidance 001, ‘Brief interventions and referral for smoking cessation in primary care and other settings’, 2006). If an individual is unable or unwilling to accept a referral they should be offered pharmacotherapy in line with recommendations from the NICE TA ‘Nicotine replacement therapy’ (NRT) and bupropion for smoking cessation’ TA39, 2002.
6.2 Introduction – lifestyle modification for the primary prevention of CVD

There is a substantive and consistent body of epidemiological, physiological and observational evidence demonstrating that dietary modification modifies blood lipids and other risk factors and these changes are associated with reductions in morbidity and mortality from CVD. Similarly epidemiological, physiological and observational evidence supports the association between cardiovascular health and levels of moderate or greater physical activity and associates a sedentary lifestyle with increased cardiovascular risk.

Differences in the prevalence of smoking between the higher and lower social classes has been estimated to account for over half the difference in the risk of premature death faced by these groups (Psaty, B. M. et al 1999).

It is however extremely difficult to design, fund or organise trials sufficiently large and rigorous that can yield evidence with cardiovascular outcomes for the effect of diet, physical activity, smoking cessation or multifactorial lifestyle interventions. To maintain consistency of reporting across both pharmacological and lifestyle interventions we have limited formal searches for evidence to randomised trials with outcomes that include cardiovascular events. Such studies are few. We have not reviewed the epidemiological, physiological, and observational studies which inform current national policies. We are aware however of the compelling literature in these areas and recommendations are also based upon this literature. We have referenced systematic reviews and have cross referred to the relevant national advice on dietary change and physical activity as appropriate.
6.3 Cardioprotective dietary advice

6.3.1 Evidence statements for cardioprotective dietary advice

<table>
<thead>
<tr>
<th>Low fat diet</th>
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<td>6.3.1.1</td>
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<td>6.3.1.2</td>
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<table>
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<tr>
<th>Increased fruit and vegetable diet</th>
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<tr>
<td>6.3.1.3</td>
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<table>
<thead>
<tr>
<th>Increased omega-3 fatty acids (dietary or supplementation)</th>
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<tr>
<td>6.3.1.4</td>
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</table>

6.3.2 Clinical effectiveness of low fat diets

No randomised controlled trials were identified in people at high risk of CVD that examined the effectiveness of low fat diet versus no change in diet for the outcomes of all cause mortality, cardiovascular mortality or cardiovascular morbidity.
One small randomised controlled trial was identified on the effectiveness of low fat diet versus no change in diet to modify lipid profiles in people at high risk of CVD (Hjerkinn, E. M. et al 2004).

The participants in this trial were a sub-sample from a population of 1,232 men aged 40-49 years selected for a previous study (Hjermann, I. et al 1981) according to the following criteria: mean serum cholesterol = 7.5 to 9.8 mmol/l, coronary risk scores (based on cholesterol, smoking and BP) in the upper quartile of the distribution and systolic BP < 150 mmHg. The sub-sample of 104 men were further selected for this trial (Hjerkinn, E. M., Sandvik, L., Hjermann, I. et al 2004) if fasting triglycerides > 2.5 mmol/l.

A total of 104 men were randomised to either the intervention group which received dietary advice over a five year period or to the control who received no advice.

Participants in the dietary intervention group were given advice to reduce total energy intake (mainly by reducing sugar, alcohol and fat), reduce saturated fat consumption and slightly increase polyunsaturated fat consumption. Participants in the intervention group also received anti-smoking advice.

After five years, the dietary intervention was found to be associated with a reduction in total cholesterol (-10.5%, 95% CI -1.5% to -11.7%) and fasting triglycerides (- 27.2, 95% CI -0.1% to -27.4%) compared with control.

6.3.3 Evidence into recommendations

Due to the lack of clinical outcome data in this trial, its small size and problems with generalisibility, it was decided by the GDG that it should be excluded and that recommendations made in the Joint British Societies’ guidelines on prevention of CVD in clinical practice (2005) would be adopted (total fat intake should be ≤ 30% of total energy intake and saturated fats should comprise ≤ 10% of total energy intake). These targets are slightly lower for total fat than those set by the Department of Heath for the general population (total fat ≤ 35% of total energy intake and saturated fats ≤ 10% of total energy intake) (Department of Health 2005).
6.3.4 Clinical effectiveness of increased fruit and vegetables diet

No randomised controlled trials were identified that compared increased fruit and vegetables diet with usual diet in people at high risk of CVD.

6.3.5 Evidence into recommendations

The GDG decided to recommend five portions of fruit and vegetables per day in line with advice given to the general population. For further information, please refer to the Department of Health paper 'Choosing a Better Diet: a food and health action plan' (Department of Health 2005), (de la Hunty, A. 1995); (Marshall, T. and Rouse, A. 2002) and the food standards agency website (Food Standards Agency 2007).

6.3.6 Clinical effectiveness of increased omega 3 fatty acids (dietary or supplementation)

No randomised controlled trials were identified that compared increased consumption of oily fish or taking omega 3 fatty acid supplements versus no change in diet in people at high risk of CVD.

6.3.7 Evidence into recommendations

The GDG considered that for dietary fish, the recommendations made by the Joint British Societies' guidelines on prevention of CVD in clinical practice (2005) should be adopted, which recommends at least two servings of omega-3 fatty acid containing fish per week. The GDG decided that there was insufficient evidence to recommend omega 3 fatty acid supplementation for people at high risk of CVD.

6.4 Plant stanols and sterols

6.4.1 Evidence statements for plants stanols and sterols

| 1.1.1.1 | No randomised controlled trials were identified in people at high risk of CVD that compared giving plant stanols and sterols with |
usual diet for the outcomes lipid modification, mortality or morbidity.

6.5 **Regular physical activity**

6.5.1 **Evidence Statements for physical activity**

6.5.1.1 No randomised controlled trials were identified in people at high risk of CVD that compared regular physical activity with sedentary lifestyle for the outcomes mortality or morbidity.

6.5.1.2 One meta-analysis in hyperlipidaemic and normolipidaemic people found that regular physical activity reduced total cholesterol, LDL cholesterol and triglyceride levels and increased HDL cholesterol levels compared with control.

6.5.1.3 Two studies found that programmes to increase physical activities were cost effective compared to no exercise programmes in improving outcomes for people at risk of CVD.

6.5.2 **Clinical effectiveness of regular physical activity**

No randomised controlled trials were identified in people at high risk of CVD that examined the effectiveness of regular physical activity versus sedentary lifestyle for the outcomes of all cause mortality, cardiovascular mortality or cardiovascular morbidity.

One meta-analysis was identified on the effectiveness of regular physical activity versus sedentary lifestyle to modify lipid profiles in hyperlipidaemic and normolipidaemic people (Halbert, J. A. et al 1999).

Included within the meta analysis were randomised controlled trials which involved an aerobic or resistance training programme of at least 4 weeks duration (mean length of exercise was 25.7 weeks, range 9-52 weeks).

Fifteen of the 31 randomised controlled trials recruited subjects classified as hyperlipidaemic (mean total cholesterol at baseline of > 5.5 mmol/l) and 16 recruited normolipidaemic subjects (mean total cholesterol < 5.5 mmol/l).
Twenty seven studies used aerobic training exclusively, three used resistance training and one used both forms of training (Halbert, J. A., Silagy, C. A., Finucane, P. et al 1999).

Total cholesterol was found to be decreased by 0.10 mmol/l more in the regular physical activity intervention group compared with the control group (95% CI 0.02 to 0.18), HDL cholesterol increased by 0.05 mmol/l more (95% CI 0.02 to 0.08), LDL cholesterol decreased by 0.10 mmol/l more (95% CI 0.02 to 0.19) and triglycerides decreased by 0.08 mmol/l more in the intervention group compared with the control group (95% CI 0.02 to 0.14) (Halbert, J. A., Silagy, C. A., Finucane, P. et al 1999).

6.5.3 Evidence into recommendations

Due to the lack of clinical outcome data in this meta-analysis, it was decided by the GDG that recommendations would be made based on those of the following documents:

- The Chief Medical Officer's report 'At least five a week: Evidence on the impact of physical activity and its relationship to health' (Chief Medical Officer 2004)
- The NICE public health intervention guidance no. 2 'Four commonly used methods to increase physical activity: brief interventions in primary care, exercise referral schemes, pedometers and community-based exercise programmes for walking and cycling' (National Institute for Health and Clinical Excellence 2007)

These guidelines recommend that thirty minutes of at least moderate intensity activity should be taken per day, at least five days a week. The chief medical officer’s report (ref) describes what is meant by moderate intensity activity: A person who is doing moderate intensity activity will usually experience:

- An increase in breathing rate
1. An increase in heart rate, to the level where the pulse can be felt, and
2. A feeling of increased warmth, possibly accompanied by sweating on hot or humid days.

Also, a bout of moderate intensity activity can be continued for many minutes without a feeling of exhaustion.

The typical activity pattern of a moderately active person would include doing one or more of the following:

- Regular active commuting on foot or by bicycle
- Regular work related physical tasks
- Regular household and garden activities
- Regular active recreation or social sport at moderate intensity.

Examples of the intensities and energy expenditures for common types of physical activity are given in Table 2.
1 Table 2

<table>
<thead>
<tr>
<th>Activity</th>
<th>Intensity</th>
<th>Intensity (METS)</th>
<th>Energy expenditure (Kcal equivalent, for a person of 60kg doing the activity for 30 minutes)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ironing</td>
<td>light</td>
<td>2.3</td>
<td>69</td>
</tr>
<tr>
<td>Cleaning and dusting</td>
<td>light</td>
<td>2.5</td>
<td>75</td>
</tr>
<tr>
<td>Walking – strolling, 2mph</td>
<td>light</td>
<td>2.5</td>
<td>75</td>
</tr>
<tr>
<td>Painting/decorating</td>
<td>Moderate</td>
<td>3.0</td>
<td>90</td>
</tr>
<tr>
<td>Walking – 3mph</td>
<td>Moderate</td>
<td>3.3</td>
<td>99</td>
</tr>
<tr>
<td>Hoovering</td>
<td>Moderate</td>
<td>3.5</td>
<td>105</td>
</tr>
<tr>
<td>Golf – walking, pulling clubs</td>
<td>Moderate</td>
<td>4.3</td>
<td>129</td>
</tr>
<tr>
<td>Badminton – social</td>
<td>Moderate</td>
<td>4.5</td>
<td>135</td>
</tr>
<tr>
<td>Tennis – doubles</td>
<td>Moderate</td>
<td>5.0</td>
<td>150</td>
</tr>
<tr>
<td>Walking – brisk, 4mph</td>
<td>Moderate</td>
<td>5.0</td>
<td>150</td>
</tr>
<tr>
<td>Mowing lawn – walking, using power-mower</td>
<td>Moderate</td>
<td>5.5</td>
<td>165</td>
</tr>
<tr>
<td>Cycling – 10-12mph</td>
<td>Moderate</td>
<td>6.0</td>
<td>180</td>
</tr>
<tr>
<td>Aerobic dancing</td>
<td>Vigorous</td>
<td>6.5</td>
<td>195</td>
</tr>
<tr>
<td>Cycling – 12 -14mph</td>
<td>Vigorous</td>
<td>8.0</td>
<td>240</td>
</tr>
<tr>
<td>Swimming – slow crawl, 50 yards per-minute</td>
<td>Vigorous</td>
<td>8.0</td>
<td>240</td>
</tr>
<tr>
<td>Tennis – singles</td>
<td>Vigorous</td>
<td>8.0</td>
<td>240</td>
</tr>
<tr>
<td>Running – 6mph (10minutes/mile)</td>
<td>Vigorous</td>
<td>10.0</td>
<td>300</td>
</tr>
<tr>
<td>Running – 7mph (8.5minutes/mile)</td>
<td>Vigorous</td>
<td>11.5</td>
<td>345</td>
</tr>
<tr>
<td>Running – 8mph (7.5 minutes/mile)</td>
<td>Vigorous</td>
<td>13.5</td>
<td>405</td>
</tr>
</tbody>
</table>

MET = Metabolic equivalent
1 MET = A person’s metabolic rate (rate of energy expenditure) when at rest
2 METs = A doubling of the resting metabolic rate

Adapted from the Chief Medical Officers (2004). Found at: www.dh.gov.uk

The chief medical officer’s report also provides useful information on the potential risks associated with physical activity. It stresses that the risks associated with taking part in physical activity at levels that promote health are low and that the health benefits far outweigh the risks. The report states that the greatest risks in terms of sustaining sports injuries are faced by:
• People who take part in vigorous sports and exercise
• People to do ‘excessive’ amounts of exercise, and
• People with existing musculoskeletal disease or at high risk of disease.

In relation to cardiovascular risk, the report states that ‘extremely rarely, inactive and unfit individuals who start doing vigorous physical activity may face increased cardiovascular risks’. In addition, it states that vigorous levels of activity may increase the risk of heart attack, although this increased risk appears to only apply to men with high blood pressure and is largely limited to people who do not exercise regularly.

6.5.4 Cost effectiveness of regular physical activity

Two studies were found which addressed this question, one Canadian (Lowensteyn, I. et al 2000) and one American (Marshall, T. et al 2005). None of the studies were done in the UK.

Study (Marshall, T., Bryan, S., Gill, P. et al 2005) was a cost utility analysis which used effectiveness data from the Framingham study. It was not clear as to the sources of the utility data they used in their decision model however it did use appropriate methodology. The authors did not provide resource use and quantities separately which makes it difficult to reproduce their work.

The authors reported that exercise resulted in 529.8 discounted QALYs over the 30 year follow up. Cost/QALY gained was $1395/QALY. A range of univariate sensitivity analyses were done, and the model was robust to all changes in assumptions that were tested.

The second study (Lowensteyn, I., Coupal, L., Zowall, H. et al 2000) was a cost effectiveness which used effectiveness data from a number of different studies published between 1980 and 1999. The authors were very detailed in their reporting and references were provided. Resource use and quantities were provided separately.
The authors reported results separately for men and women and stratified results into three age groups. The results showed that exercise, especially unsupervised exercise was a cost effective intervention compared to no exercise. The benefits were more for younger men and less in the elderly man and women. The cost per life year gained ranged between $645/LYG for the 35-54 year age group in unsupervised men to $30704 in the 65-74 year age group attending supervised sessions. For women the incremental cost effectiveness ratios for women ranged between $4915 to $ 87166 respectively.

In conclusion, a programme to increase physical activity compared to no programme is cost effective in improving outcomes for people at risk of CVD. The results from the two studies showed that younger men benefit more from such programmes than older men and women. Results also showed that unsupervised activity is more cost effective than supervised classes. This however depended on the assumption that there is almost 100% adherence to the exercise programme.
6.6 Combined cardioprotective dietary advice and regular physical activity

6.6.1 Evidence statements for combined cardioprotective dietary advice and regular physical activity

6.6.1.1 No randomised controlled trials were identified in people at high risk of CVD that compared combined cardioprotective dietary advice and regular physical activity with usual lifestyle for the outcomes mortality or morbidity.

6.6.1.2 One randomised controlled trial in people at high risk of CVD found that a combination of low fat diet and aerobic exercise was associated with a reduction in total cholesterol and triglycerides and an increase in HDL cholesterol levels compared with control.

A second randomised controlled trial found that a combination of low fat diet and aerobic exercise was associated with a reduction in total cholesterol and LDL cholesterol compared with usual diet.

A third randomised controlled trial found that a combination of diet and aerobic exercise was not associated with a change in lipid levels compared with control.

6.6.2 Clinical effectiveness of combined cardioprotective dietary advice and regular physical activity

No randomised controlled trials were identified in people at high risk of CVD that examined the effectiveness of dietary advice versus usual diet and / or regular physical activity versus sedentary lifestyle for the outcomes of all cause mortality, cardiovascular mortality or cardiovascular morbidity.

Three randomised controlled trials were identified which examined the effectiveness of diet, regular physical activity and the combination of both interventions to improve...
serum lipid level profiles in people with elevated CVD risk factors (Anderssen, S. A.
et al 1995); (Hellenius ML et al 1993); (Stefanick, M. L. et al 1998).

The first study was a randomised controlled trial of six months duration in 158
healthy men aged 35 to 60 years with moderately elevated CVD risk factors.
(Hellenius ML, de Faire U, Berglund B et al 1993). Participants were randomised to
one of three intervention groups or to the control group (usual lifestyle). The first
intervention was diet whereby participants were given verbal and written dietary
advice that total fat consumption should comprise no more than 30% of energy
intake, saturated fat no more than 10% of energy, cholesterol consumption should
be less than 300 mg/day, polyunsaturated fat up to 10% of energy, monounsaturated
fat 10-15% energy, carbohydrates (mainly complex) 50-60% energy and protein 10-
20% energy.

The second intervention was physical activity; participants were given verbal and
written advice to take regular physical activity of an aerobic type 2-3 times per week
for 30-45 minutes at 60-80% maximum heart rate.

The third intervention was a combination of diet and physical activity. The control
group was told to continue with the diet and lifestyle as prior to joining the study.

After six months, lipid levels were measured and no significant differences were
found in total cholesterol, LDL cholesterol or HDL cholesterol for any of the
intervention groups compared to control.

The second study was a randomised controlled trial (Anderssen, S. A., Haaland, A.,
Participants who each had several coronary risk factors were recruited in Oslo and
were then randomised to one of three intervention groups or to the control group.
The dietary intervention consisted of counseling to reduce intake of saturated fat and
cholesterol and to consume more fish. Energy restriction advice was given to those
overweight.

For the physical activity intervention, participants attended aerobic exercise sessions
3 times per week for one hour where they exercised at 60-80% of their peak heart
rate in supervised classes of 14 to 20 people.
The third intervention group was a combination of diet and physical activity as already described. The control group was told not to change their lifestyle during the trial but as all the other participants they were advised against smoking.

After one year, no significant differences in total, LDL or HDL cholesterol were observed for the diet only or physical activity only interventions compared to control. For the combined diet and physical activity intervention, a significant decrease in total cholesterol and a significant increase in HDL cholesterol were observed compared to control. In addition, triglycerides were found to be significantly reduced in all three intervention groups compared to control.

The final randomised controlled trial (Stefanick, M. L., Mackey, S., Sheehan, M. et al 1998) was of one year duration and included 197 men and 180 postmenopausal women. Women were 45 to 64 years of age, had HDL cholesterol levels < 1.55 mmol/l, and LDL cholesterol levels between 3.23 and 5.42 mmol/l. Men were 30 to 64 years of age, had HDL cholesterol levels < 1.14 mmol/l, and LDL cholesterol levels between 3.23 and 4.90 mmol/l.

Participants were randomised to one of three intervention groups or to the control group. The first intervention was diet where participants were advised to follow the National Cholesterol Education Program (NCEP) Step 2 diet: total fat less than 30% of energy intake, saturated fat less than 7% of energy and cholesterol less than 200 mg per day.

The second intervention was aerobic exercise: participants attended 6 weeks of supervised 1 hour sessions, 3 times per week (held separately for groups 2 and 3). For the remaining 7 to 8 months of the trial, they could attend supervised classes and / or undertake home-based activities with the goal of engaging in aerobic activity equivalent to at least 16km of brisk walking or jogging each week.

The control group were asked to maintain their usual diet and exercise habits.

After one year, for both men and postmenopausal women, significant decreases in total and LDL cholesterol levels were observed in the diet plus physical activity intervention group compared to control.
In addition, one systematic review was identified that assessed the effectiveness of multiple risk factor interventions which included smoking cessation, physical activity and dietary advice with or without pharmacological intervention on a number of outcomes including all cause and CHD mortality (Ebrahim, S. et al. 2006). A total of 39 randomised controlled trials were identified in adults of ≥ 40 years of age from general populations, workforce populations and high risk groups. Ten of these trials reported clinical event data and a meta-analysis of these ten trials found that multiple risk factor interventions were not associated with a reduction in total or coronary heart disease (CHD) mortality.

The conclusion of the review was that ‘The pooled effects suggest multiple risk factor intervention has no effect on mortality. However, a small but potentially important benefit of treatment (about a 10% reduction in CHD mortality) may have been missed. Risk factor changes were relatively modest, were related to the amount of pharmacological treatment used, and in some cases may have been over-estimated because of regression to the mean effects, lack of intention to treat analysis, habituation to blood pressure measurement, and use of self-reports on smoking.’

6.6.3 Evidence into recommendations

Due to the lack of evidence on the effectiveness of combined approaches, it was decided by the GDG that cardioprotective dietary advice and regular physical activity interventions would be considered separately.

6.6.4 Cost effectiveness of combined cardioprotective dietary advice and regular physical activity

There were no cost effectiveness studies found surrounding the use of combined dietary advice and regular physical activity in the prevention of CVD.

6.7 Weight management

For guidance in weight management in people at high risk of CVD refer to the NICE guideline:

6.8 Smoking cessation

For guidance on smoking cessation refer to the NICE Technology appraisal:

- Smoking cessation - bupropion and nicotine replacement therapy. The clinical effectiveness and cost effectiveness of bupropion (Zyban) and Nicotine Replacement Therapy for smoking cessation TA039 (2002).

And also the NICE Public health intervention guidance:

- Brief interventions and referral for smoking cessation in primary care and other settings PHI001, (2006).
7 Drug therapy for the primary prevention of cardiovascular disease (CVD)

7.1 Recommendations for drug therapy

7.1.1 Overall drug therapy recommendation

7.1.1.1 When considering therapy for lipid modification all modifiable risk factors should be considered and their management optimised. Assessment should include evaluation of the following:

- smoking status
- blood pressure
- body mass index or other measure of obesity, (refer to NICE Obesity guideline, No CG43, 2006)
- fasting total cholesterol, LDL cholesterol, HDL cholesterol and triglycerides
- fasting blood glucose
- renal function
- liver function (transaminases).

Secondary causes of dyslipidaemia should be considered and excluded before starting lipid therapy. This should include measurement of TSH.

7.1.2 Statins recommendations

7.1.2.1 Statin therapy is recommended as part of the management strategy for the primary prevention of CVD in adults who have a 20% or greater 10-year risk of developing CVD. This level of risk
should be estimated using the recommended CVD risk equations or by clinical assessment in people for whom these are not available or appropriate (for example people over 75 years).

| 7.1.2.2 | When the decision has been made to prescribe a statin, it is recommended that therapy should usually be initiated with a drug with a low acquisition cost (taking into account required daily dose and product price per dose). |
| 7.1.2.3 | Simvastatin 40 mg or pravastatin 40 mg, or a drug of comparable effectiveness and acquisition cost, is recommended as the treatment. |
| 7.1.2.4 | A lower dose or alternative preparation may be appropriate depending upon tolerability and clinical circumstance. |
| 7.1.2.5 | Higher intensity statins should not routinely be offered to people for primary prevention. |
| 7.1.2.6 | A target for total or LDL cholesterol is not recommended for people who are treated with a statin. |
| 7.1.2.7 | Routine monitoring of creatine kinase is not recommended in asymptomatic patients who are being treated with a statin. |
| 7.1.2.8 | People who are being treated with a statin should be advised to seek medical advice if they develop muscle symptoms (pain, tenderness or weakness). If this occurs creatine kinase should be measured. |
| 7.1.2.9 | Any statin may need to have the dose reduced or be temporarily or permanently stopped if other drugs are introduced or treatment is required for a concomitant illness that interferes with metabolic pathways or increases the propensity for drug and food interactions. |
7.1.2.10 Baseline liver enzymes should be measured before starting a statin. Liver function enzymes should be measured within six months of starting treatment and again at 12 months but not again unless clinically indicated.

7.1.2.11 People who have raised liver enzymes (transaminases) should not routinely be excluded from statin therapy.

7.1.2.12 Statins should be discontinued in people who develop an unexplained peripheral neuropathy and further advice from a specialist should be sought.

1 7.1.3 Fibrates recommendations

7.1.3.1 Fibrates should not routinely be recommended for primary prevention of CVD.

Where statins are not tolerated, fibrates may be considered.

2 7.1.4 Nicotinic acid recommendations

7.1.4.1 Nicotinic acid is not recommended for primary prevention of CVD.

3 7.1.5 Anion exchange resin recommendations

7.1.5.1 Anion exchange resins should not routinely be recommended for primary prevention of CVD.

Where statins are not tolerated, an anion exchange resin licensed for primary prevention of CVD may be considered.

4 7.1.6 Ezetimibe recommendations

7.1.6.1 Please refer to NICE Technology Appraisal No. XX ‘Ezetimibe for the treatment of primary (heterozygous familial and non-familial)
7.1.7 Combination drug therapy

7.1.7.1 The combination of an anion-exchange resin, ezetimibe, fibrate or nicotinic acid with a statin is not recommended for primary prevention of CVD.

7.1.7.2 The combination of a fish oil supplement with a statin is not recommended for primary prevention of CVD.

7.2 Introduction to drug therapy for the primary prevention of CVD

This chapter considers pharmacological treatments for people whose 10 year risk of developing CVD is greater than 20% but who have not yet experienced an event. People with diabetes or familial lipid disorders are excluded from these recommendations and are considered in alternative NICE guidance.

Statins are the drug of first choice for the primary prevention of CVD as they are more effective at lowering LDL cholesterol than other drugs currently licensed for primary prevention and have been shown to have a greater impact on clinical outcome.

The NICE Technology Appraisal (NICE technology appraisal guidance 94, ‘Statins for the prevention of cardiovascular events’ 2006) has thoroughly and comprehensively reviewed the evidence on the effectiveness and cost effectiveness of statins and our recommendations on the initiation of statin therapy are based upon this report (National Institute for Health and Clinical Excellence 2006).

The NICE Technology Appraisal recommends statin therapy as part of the management strategy for the primary prevention of CVD for adults who have a 20% or greater 10-year risk of developing CVD. This may result in more than half of the men aged over 50 years and 20% of the women over 65 years being considered for lipid lowering therapy.
The routine use of higher intensity statins has not been recommended for primary prevention. Neither has this guideline recommended the use of cholesterol targets for primary prevention. Treatment targets are considered further in the secondary prevention drug therapy chapter (Section 9.3.8).

This guideline has not made a detailed study of the safety of statins which is the proper concern of other regulatory agencies but has considered evidence from one systematic review and two meta-analyses of statin safety. Statins are generally well tolerated and the occurrence of serious adverse events are rare especially at the doses used for primary prevention.

Before the licensing of statins, fibrates were one of the mainstays of lipid modification, usually for people with established CVD. Their use for primary prevention was controversial and the failure to demonstrate reductions in total mortality in the 1978 cooperative World Health Organisation primary prevention trial (World Health Organization. 1978) and the 1987 Helsinki Heart Study (Frick, M. H. et al 1987) led to concerns about the effectiveness of fibrates.

Anion exchange resins were also used as first line agents for the management of dyslipidaemia and in secondary prevention before the advent of statins. The 1984 Lipid Research Clinics coronary primary prevention trial (1984) was an early trial of effectiveness with significant reductions in cardiovascular endpoints but no significant difference in total mortality.

In the last 20 years little further progress has been made on randomised trials with cardiovascular outcomes testing the effectiveness of fibrates or anion exchange resins for primary prevention.
## 7.3 Statins

### 7.3.1 Evidence statements for statins

<table>
<thead>
<tr>
<th>Statin therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>7.3.1.1</strong> For people without clinical evidence of CVD at study entry, a meta-analysis found that statin therapy was associated with a reduction in the risk of fatal MI and nonfatal MI and the composite outcomes of CHD death and nonfatal MI, and CHD death, nonfatal MI, fatal or nonfatal stroke and coronary revascularization compared with placebo. For people without clinical evidence of CHD at study entry, a meta-analysis found that statin therapy was associated with a reduction in the risk of all-cause mortality, fatal MI, nonfatal MI and stable angina and the composite outcomes of CHD death and nonfatal MI, and CHD death, nonfatal MI, fatal or nonfatal stroke and coronary revascularization compared with placebo.</td>
</tr>
<tr>
<td><strong>7.3.1.2</strong> No randomised controlled trials were identified that compared higher intensity statin therapy with lower intensity therapy in people at high risk of CVD.</td>
</tr>
<tr>
<td><strong>7.3.1.3</strong> The NICE Statin TA94, concluded that statin treatment in patients with CVDs is cost effective compared with no statin treatment (NICE Technology Appraisal guidance, ‘Statins for the prevention of cardiovascular events’ TA 94, 2006)</td>
</tr>
</tbody>
</table>

### Adverse events
### 7.3.1.4
In a systematic review of cohort studies, randomised trials, voluntary notifications to regulatory authorities and published case reports, the incidence of major adverse events was low.

Incidence of rhabdomyolysis was estimated at 3.4 per 100,000 person years (this rose to 4.2 per 100,000 person years in patients treated with statins which are metabolised by cytochrome P450 3A4 and was ten fold higher when a statin was combined with gemfibrozil).

Statin therapy was not found to be associated with a significant increase in the incidence of raised creatine kinase. Incidence of myopathy was estimated at 11 per 100,000 person years and incidence of peripheral neuropathy was estimated at 12 per 100,000 person years.

Elevations of the liver enzymes alanine aminotransferase and/or aspartate aminotransferase were reported more frequently in those treated with statins compared with placebo, especially at higher doses. Trials showed no excess of liver disease or renal disease in statin allocated participants.

### 7.3.1.5
A meta-analysis of data from 18 randomised controlled trials found statin therapy to be associated with a greater odds of any adverse event compared with placebo. A number needed to harm (NNH) analysis was performed and compared to placebo the number of people that would need to be treated with a statin to observe any statin-related adverse event was 197 people, to observe a statin-related rhabdomyolysis was 7,428 people and to observe statin-related rhabdomyolysis or creatine phosphokinase > 10 x upper limit of normal was 3,400 people.

### 7.3.1.6
A meta-analysis of 26 randomised controlled trials showed cancer incidence and cancer death to be unaffected by statin therapy. A subgroup analysis by cancer type also found no effect of statin
7.3.2 Clinical effectiveness of statins

Throughout the guideline, we have reported 95% confidence intervals for relative risks (RR) and odds ratios (OR). Where the 95% confidence interval crosses the 'line of no effect' i.e., when the confidence intervals included 1, we have interpreted this as being non-significant. This interpretation holds even when the upper or lower limit of the confidence interval is 1.00.

The NICE Technology Appraisal (National Institute for Health and Clinical Excellence 2006) entitled 'Statins for the prevention of cardiovascular events' 2006 states that:

- Statin therapy is recommended as part of the management strategy for the primary prevention of CVD for adults who have a 20% or greater 10-year risk of developing CVD.

The recommendation was based upon assessment of the effectiveness of statin therapy in people without clinical evidence of CVD at study entry and in people without clinical evidence of coronary heart disease (CHD) at study entry (some or all of whom had other CVD at study entry).

Two randomised controlled trials were identified that compared statin therapy with placebo in people without clinical evidence of CVD at study entry; CAIUS (Mercuri, M. et al 1996) and CARDS (Colhoun, H. M. et al 2004), and a further three randomised controlled trials were identified that presented subgroup analyses for people without CVD; ASCOT-LLA (Sever, P. S. et al 2003), PROSPER (Shepherd, J. et al 2002) and WOSCOPS (Shepherd, J. et al 1995).

A meta-analysis was conducted that included data from three of these trials, two of which used pravastatin 40 mg (CAIUS (Mercuri, M., Bond, M. G., Sirtori, C. R. et al 1996) and PROSPER (Shepherd, J., Blauw, G. J., Murphy, M. B. et al 2002)) and one used atorvastatin 10 mg (CARDS (Colhoun, H. M., Betteridge, D. J., Durrington, P. N. et al 2004)). Subgroup data from the ASCOT-LLA (Sever, P. S., Dahlof, B., Poulter, N. R. et al 2003) and WOSCOPS (Shepherd, J., Cobbe, S. M., Ford, I. et al 1995) trials was presented in a form that meant it could not be included in the meta-analysis. The meta-analysis found that statin therapy was associated with a
reduction in the risk of fatal MI (RR 0.41, 95% CI 0.19 to 0.88), nonfatal MI (RR 0.60, 95% CI 0.37 to 0.97) and the composite outcomes of CHD death and nonfatal MI (RR 0.66, 95% CI 0.46 to 0.96) and of CHD death, nonfatal MI, fatal or nonfatal stroke and coronary revascularization (RR 0.64, 95% CI 0.48 to 0.84). Statin therapy was not found to be associated with a reduction in the risk of the following outcomes; all-cause mortality, cardiovascular mortality, CHD mortality, stroke mortality, nonfatal stroke, unstable angina and revascularisation (National Institute for Health and Clinical Excellence 2006).

Four randomised controlled trials were identified that compared statin therapy with placebo in people without clinical evidence of CHD at study entry CAIUS (Mercuri, M., Bond, M. G., Sirtori, C. R. et al 1996), CARDS (Colhoun, H. M., Betteridge, D. J., Durrington, P. N. et al 2004), DALI (Diabetes Atorvastin Lipid Intervention 2001) and ASCOT-LLA (Sever, P. S., Dahlof, B., Poulter, N. R. et al 2003)). A further three randomised controlled trials were identified that presented subgroup analyses for people without CHD PROSPER (Shepherd, J., Blauw, G. J., Murphy, M. B. et al 2002), WOSCOPS (Shepherd, J., Cobbe, S. M., Ford, I. et al 1995) and HPS (Heart Protection Study Collaborative Group. 2002)).

A meta-analysis was conducted that included data from six of these trials, two of which used pravastatin 40 mg CAIUS (Mercuri, M., Bond, M. G., Sirtori, C. R. et al 1996) and PROSPER (Shepherd, J., Blauw, G. J., Murphy, M. B. et al 2002)), one used simvastatin 40 mg HPS (Heart Protection Study Collaborative Group. 2002)) and three used atorvastatin 10 mg ASCOT-LLA (Sever, P. S., Dahlof, B., Poulter, N. R. et al 2003) CARDS (Colhoun, H. M., Betteridge, D. J., Durrington, P. N. et al 2004), DALI (Diabetes Atorvastin Lipid Intervention 2001)). Subgroup data from the WOSCOPS trial was presented in a form that meant it could not be included in the meta-analysis. The meta-analysis found that statin therapy was associated with a reduction in the risk of all-cause mortality (RR 0.83, 95% CI 0.70 to 0.98), fatal MI (RR 0.41, 95% CI 0.19 to 0.88), nonfatal MI (RR 0.58, 95% CI 0.36 to 0.94) and stable angina (RR 0.59, 95% CI 0.38 to 0.90) and the composite outcomes of CHD death and nonfatal MI (RR 0.64, 95% CI 0.50 to 0.82) and CHD death, nonfatal MI, fatal or nonfatal stroke and coronary revascularization (RR 0.73, 95% CI 0.63 to 0.86). Statin therapy was not found to be associated with a reduction in the risk of
the following outcomes: cardiovascular mortality, CHD mortality, stroke mortality, nonfatal stroke, PAD, unstable angina and revascularisation.

Results from the largest primary prevention study (n = 10,305) (ASCOT-LLA (Sever, P. S., Dahlof, B., Poulter, N. R. et al. 2003), which compared atorvastatin with placebo over approximately 3 years, suggested that the number needed to treat (NNT) to avoid either a death from CHD or a nonfatal MI, in people without existing CHD, was 95 (95% CI 60 to 216).

The NICE Technology Appraisal also considered whether statins differ in their relative effectiveness in the following population subgroups: In women compared with men at a similar level of cardiovascular risk; in people with diabetes compared to people without diabetes; or in people aged over 65 years compared with people aged under 65 years. Evidence from placebo-controlled trials showed that statins do not differ in their relative effectiveness in these subgroups. No placebo-controlled trials were identified that provided information relating to people from different ethnic groups.

The NICE Technology Appraisal (National Institute for Health and Clinical Excellence 2006) states further that:

- When the decision has been made to prescribe a statin, it is recommended that therapy should usually be initiated with a drug of low acquisition cost (taking into account required daily dose and product price per dose).

Cost effectiveness analysis indicates that simvastatin 40 mg and pravastatin 40 mg are both cost effective options for the primary prevention of CVD and the GDG considered that they were the most effective preparations at the lowest acquisition cost.

7.3.2.1 **High intensity versus standard intensity statin therapy**

No randomised controlled trials were identified that included cardiovascular events and compared higher intensity statin therapy with lower intensity therapy in people at high risk of CVD. The GDG thus considered it was inappropriate to routinely recommend their use for the primary prevention of CVD.
7.3.2.2 **Cholesterol ‘targets’**

There are no clinical trials in primary prevention that have evaluated the relative and absolute benefits of cholesterol lowering to different total and LDL cholesterol targets in relation to clinical events. In addition, the clinical effectiveness of higher intensity statins and of combining statins with other lipid lowering drugs has yet to be demonstrated for primary prevention. It was decided that due to the lack of evidence, this guideline would not recommend the use of target levels of cholesterol for people at high risk of CVD. This is discussed further under the drug therapy secondary prevention (section 9.3.8).

7.3.2.3 **Adverse events associated with lower intensity statin therapy**

Three papers were identified on the adverse events associated with lower intensity statin therapy. Two papers reviewed and meta-analysed all adverse events (especially those connected with skeletal muscle and liver) (Law, M. and Rudnicka, A. R. 2006) (Silva, M. A. et al 2006) and one examined statin usage and the risk of cancer (Dale, K. M. et al 2006).

It was noted by the GDG that there are limitations associated with these studies which may result in underestimation of adverse events. Firstly, all randomised controlled trials which have examined the effectiveness of statin therapy excluded some potential participants and a number of randomised controlled trials have also included a pre-randomisation run-in phase during which participants were treated with an open label statin. At the end of this time, some chose not to enter the trial or had some other reason not to do so. Thus, tolerability may be better and the incidences of adverse events lower in the trials than in unselected patients.

Secondly, trials may not necessarily report all side effects that are experienced, although it is likely that serious side effects are reported. Thirdly, the duration of randomised controlled trials may be shorter than the lag time expected for cancer manifestation.

The first study was a systematic review of cohort studies, randomised trials, voluntary notifications to voluntary regulatory authorities and published case reports (Law, M. and Rudnicka, A. R. 2006). The incidence of rhabdomyolysis was estimated from the cohort studies: for statins other than cerivastatin was 3.4 (95% CI
1.6 to 6.5) per 100,000 person years, with a case fatality of 10%. The rates were about 10 times higher for cerivastatin and also for statins other than cerivastatin when taken with gemfibrozil. For cerivastatin taken with gemfibrozil, the incidence was 2,000 times higher, an absolute annual incidence of about 10%. Cerivastatin was withdrawn because of this unacceptable risk of serious side effects. In contrast there were no incidences of rhabdomyolysis with pravastatin or fluvastatin (which are not oxidised by CYP3A4) and the mean incidence of rhabdomyolysis among those taking lovastatin, simvastatin or atorvastatin (which are oxidised by cytochrome P450 3A4 (CYP3A4)) was 4.2 (95% CI 1.9 to 8.0) per 100,000 person years. This difference was not statistically significant because relatively few person-years of follow-up were recorded for fluvastatin and pravastatin.

The mean incidence of myopathy in patients treated with statins was 11 per 100,000 person years (estimated from cohort studies, supported by randomised trials). There was no significant difference in the incidence of a raised creatine kinase to $\geq 10 \times$ ULN on a single measurement during routine monitoring between participants in 13 trials allocated to a statin compared to those allocated placebo (83 per 100,000 person years of statin treatment versus 60 per 100,000 person years with placebo). In two trials none had creatine kinase elevated on 2 consecutive measurements (Law, M. and Rudnicka, A. R. 2006).

The incidence of liver disease attributable to statin therapy is rare. In 3 randomised trials of pravastatin, both gall bladder and hepatobiliary disorders were less common in patients allocated statins than in those allocated placebo. Elevations in alanine aminotransferase and or aspartate aminotransferase were reported more frequently in patients treated with statins than with placebo, and elevations of alanine aminotransferase (defined as $\geq 3$ times the ULN, or 120 units/l) were found in 300 statin-allocated and 200 placebo-allocated participants per 100,000 person-years. However, statistical heterogeneity across the trials was noted. An elevated alanine aminotransferase on 2 consecutive measurements was found in 110 participants allocated to a statin and in 40 participants allocated to placebo per 100,000 person-years. Elevations in alanine aminotransferase were reported more frequently with higher doses of statin. The systematic review reported that in 100,000 person-years of statin use, denying 300 persons with elevated alanine aminotransferase the
benefit of a statin (or 110 persons if repeat measures were used) would prevent liver
disease in less than 1 person (Law, M. and Rudnicka, A. R. 2006).

Randomised trials showed no excess of renal disease or proteinuria in statin
allocated participants. There is evidence that statins cause peripheral neuropathy
but the attributable risk is small (12 per 100,000 person years estimated from cohort
studies and case reports). No change in cognitive function was found in trials of

The second study was a meta-analysis (Silva, M. A., Swanson, A. C., Gandhi, P. J.
et al 2006) which analysed data from 18 randomised controlled trials published in
the last 11 years. The total number of participants randomised to receive a statin
was 36,062 and to receive placebo was 35,046. Trials ranged in duration from 6
weeks to 317 weeks. Simvastatin or pravastatin comprised 85.8% of the cumulative
statin exposure. Statin therapy was found to be associated with a greater odds of
any adverse event compared with placebo (OR 1.17, 95% CI 1.06 to 1.28). A
number needed to harm (NNH) analysis was also performed. The NNH (over 1 year)
was 197. for any adverse event (which included myopathy-related events (myalgia,
myopathy or asthenia), creatine phosphokinase elevation, elevated liver function
tests > 3 x ULN or rhabdomyolysis), absolute risk was calculated at 0.51% (95% CI
0.29% to 0.73%). Thus 197 people would need to be treated for 1 adverse event.
For non-serious adverse events (excludes rhabdomyolysis and creatine
phosphokinase > 10 X ULN), the NNH was 209 people (over one year), absolute risk
= 0.48% (95% CI 0.25% to 0.70%). Rhabdomyolysis was rare; the NNH was 7428
people (7428 people would have to be treated over 1 year for one event), and the
absolute risk was 0.01% (95% CI -0.01% to 0.03%). The incidence of
rhabdomyolysis or creatine phosphokinase > 10 X ULN was also rare with a NNH of
3400 people and an absolute risk of 0.03% (95% CI -0.03% to 0.09%).

The third study was a meta-analysis (Dale, K. M., Coleman, C. I., Henyan, N. N. et al
2006) which examined statin usage and the risk of cancer. Twenty six randomised
controlled trials were included (n = 86,936 participants). The number of participants
ranged between 151 and 20,536 and the duration of patient follow-up for cancer
ranged from 1.9 years to 10.4 years. Cancer incidence was found to be unaffected
by statin therapy (OR 1.02, 95% CI 0.97 to 1.07), based on 20 studies, and cancer
death was similarly unaffected (OR 1.01, 95% CI 0.93 to 1.09), based on 19 studies.
A subgroup analysis by cancer type (breast, prostate, gastrointestinal, colon,
respiratory and melanoma) was performed which also showed a neutral effect of
statin therapy.

7.3.3 Cost effectiveness of statins
The NICE Technology Appraisal (National Institute for Health and Clinical Excellence
2006) states further that:

- When the decision has been made to prescribe a statin, it is recommended
  that therapy should usually be initiated with a drug of low acquisition cost
  (taking into account required daily dose and product price per dose).

Three further cost effectiveness analysis published after the TA were identified. Two
of them compared pravastatin 40mg with placebo, Tonkin (Tonkin AM, Eckermann S
White 2006), Nagata-Kobayashi (Nagata-Kobayashi, S. et al 2005) and concluded
that pravastatin 40 mg is a cost effective option for the primary prevention of CVD
especially for the high risk group. Nagata-Kobayashi (Nagata-Kobayashi, S.,
Shimbo, T., Matsui, K. et al 2005) found that pravastatin 40 mg was not cost
effective in low risk patients compared with placebo. The third study by Lindgren
(Lindgren, P. et al 2005) compared Atorvastatin 10 mg with placebo in the
prevention of coronary and stroke events using data from the Anglo-Scandinavian
Cardiac Outcomes Trial-lipid lowering arm (ASCOT-LLA (Sever, P. S., Dahlof, B.,
Poulter, N. R. et al 2003)). They found that Atorvastatin 10mg was cost effective
with an estimated ICER of about £7349 per event avoided. There was an average of
97 events per 1000 patients in the treatment group at an additional cost of £260 per
patient compared to 132 events per 1000 patients in the placebo group. The study
was well conducted and used appropriate methodology. The findings were robust in
sensitivity analysis. They provided a cost per life year gained in their discussion
which is a better measure of cost effectiveness than the cost per event avoided they
used in their main analysis.

In conclusion lower intensity statins are cost effective. Following the NICE
Technology Appraisal (National Institute for Health and Clinical Excellence 2006),
statins with lowest acquisition cost should be used for treatment in primary prevention. The GDG based its recommendation not to recommend higher intensity statins for primary prevention on the lack of trial evidence of benefit from a reduction of cardiovascular events. A cost effectiveness analysis was therefore not considered appropriate. This decision was made on a majority basis.

7.3.4 Evidence to recommendations – statins

The NICE Technology Appraisal (National Institute for Health and Clinical Excellence 2006) review confirms that for primary prevention, statins are effective in reducing fatal and nonfatal MI and the composite outcome CHD death or nonfatal MI, fatal and nonfatal stroke and revascularisation. In trials predominantly comprising primary prevention but including a minority of people with established CVD, meta-analysis found that statin therapy was associated with a reduction in the risk of all-cause mortality, fatal and nonfatal MI and the composite outcomes of CHD death, nonfatal MI, fatal or nonfatal stroke and coronary revascularization. For primary prevention lower intensity statins are safe and cost-effective and there is trial evidence of cardiovascular benefit and low acquisition cost for simvastatin 40 mg and pravastatin 40 mg.
7.4 Fibrates

7.4.1 Evidence Statements for fibrates

7.4.1.1 One randomised controlled trial in men with elevated non-HDL cholesterol found that gemfibrozil therapy was associated with a reduction in the incidence of the combination of fatal and nonfatal MI and cardiac death compared with placebo. Gemfibrozil therapy was not associated with a reduction in total mortality compared with placebo.

7.4.1.2 One randomised controlled trial in men with elevated total cholesterol found that clofibrate therapy was associated with a reduction in the incidence of the combination of fatal ischaemic heart disease and nonfatal MI compared with placebo. Analysis of the individual components of this endpoint found that clofibrate therapy was associated with a reduction in nonfatal MI compared with placebo but not fatal ischaemic heart disease.

Clofibrate therapy was found to be associated with an increase in all cause mortality compared with placebo.

7.4.2 Clinical effectiveness of fibrates

Two randomised controlled trials were identified that compared fibrate therapy with placebo in people at high risk of CVD (World Health Organization. 1978).

The first randomised controlled trial (World Health Organization. 1978) recruited healthy men aged 30 to 59 years on the basis of their serum cholesterol levels. A total of 15,745 participants were stratified according to their total cholesterol level and randomised to one of three groups (one intervention group and two control groups):

1. Intervention group: Men with a mean total cholesterol level of 6.45 +/- 0.01 mmol/l chosen at random from the upper third of the total cholesterol distribution were allocated to receive clofibrate 1.6 g daily.
2. High cholesterol control group: Men with a mean total cholesterol level of 6.40 +/- 0.01 mmol/l chosen at random from the upper third of the total cholesterol distribution were allocated to receive placebo (olive oil capsules).

3. Low cholesterol control group: Men with a mean total cholesterol level of 4.69 +/- 0.01 mmol/l chosen at random from the lowest third of the total cholesterol distribution were allocated to receive placebo (olive oil capsules).

The trial was conducted in three European centres: Prague, Budapest and Edinburgh and participants were followed up for 5 years. Clofibrate therapy was associated with a reduction in the incidence of the combination of fatal ischaemic heart disease and nonfatal MI compared with the high cholesterol control group (167/5331 group 1 versus 208/5296 group 2, \(P < 0.05\)). When the individual components of this endpoint were analysed separately, clofibrate therapy was found to be associated with a reduction in nonfatal MI (131/5331 group 1 versus 174/5296 group 2, \(P < 0.05\)) whereas no difference was found for the outcome of fatal ischaemic heart disease (World Health Organization. 1978).

Clofibrate therapy was found to be associated with an increase in all cause mortality compared with the high cholesterol control group (162/5331 group 1 versus 127/5296 group 2, \(P < 0.05\)). The results were also analysed separately by cause of death and clofibrate therapy was found to be associated with an increase in mortality from ‘other medical causes’ (16/5331 group 1 versus 5/5296 group 2, \(P < 0.05\)), ‘all causes other than IHD’ (108/5331 group 1 versus 79/5296 group 2, \(P < 0.05\)) and ‘all causes other than IHD, Vascular and Accidents and Violence’ (77/5331 group 1 versus 47/5296 group 2, \(P < 0.01\)) compared with the high cholesterol control group. There was no difference in the numbers of deaths due to ischaemic heart disease, ‘other vascular causes or accidents’ and violence between groups 1 and 2. This initial analysis was not conducted on an intention to treat basis, however, a reanalysis on an intention to treat basis reported by the authors confirmed a significant 30% excess in standardized death rates from all causes in the clofibrate arm; Group 1 236/5331 versus Group 2 181/5296 \(P < 0.01\) (Heady, J. A., Morris, J. N., and Oliver, M. F. 1992).
The cholecystectomy rate for gall stones was higher in group 1 (rate 2.1 per 1000 p.a, \( P < 0.001 \)) compared with groups 2 (rate 0.9 per 1000) and 3 (rate 0.9 per 1000) (World Health Organization. 1978).

This trial was one of the first large randomised controlled trials to be conducted and had some caveats. Olive oil capsules were given which are not considered a true placebo. The initial analysis was not conducted on a conventional intention to treat basis, however subsequent analysis on this basis was provided (Heady, J. A., Morris, J. N., and Oliver, M. F. 1992).

It should be noted that clofibrate has now been withdrawn from the British National Formulary.

The second randomised controlled trial (Frick, M. H., Elo, O., Haapa, K. et al 1987) recruited asymptomatic men aged 40 to 55 years with dyslipidaemia (non-HDL cholesterol levels of \( \geq 5.2 \text{ mmol/l} \) on two successive measurements). A total of 4081 participants were randomised to receive either gemfibrozil or placebo and were followed up for five years. In addition, both groups were given advice to adopt a cholesterol-lowering diet, to increase physical activity and to reduce smoking and body weight.

Gemfibrozil therapy was associated with a 34% reduction (95% CI 8.2% to 52.6%) in the incidence of the combination outcome of fatal and nonfatal MI and cardiac death. After five years, the number of definite cardiac events in the gemfibrozil group was 56/2051 (an incidence rate of 27.3 per 1000) compared with 84/2030 in the placebo group (an incidence rate of 41.4 per 1000). There were no differences between groups in the total mortality rate.

Gemfibrozil therapy was associated with an increase in HDL cholesterol compared with baseline during the first year of more than 10%, this was followed by a small decline in HDL cholesterol with time. Gemfibrozil therapy was also associated with initial reductions in the levels of total cholesterol (11%), LDL cholesterol (10%), non-HDL cholesterol (14%) and triglycerides (43%). These changes were followed by a consistent level of total and LDL cholesterol and a small increase in triglyceride levels during the remaining time. Cholesterol levels did not differ significantly from
baseline during the study in those allocated placebo (Frick, M. H., Elo, O., Haapa, K. et al 1987).

During the first year, 11.3% of those randomised to receive gemfibrozil and 7% of those receiving placebo reported moderate to severe upper gastrointestinal symptoms ($P < 0.001$). During subsequent years, these rates decreased to 2.4% for the gemfibrozil group and 1.2% for the placebo group ($P < 0.05$). No significant difference between treatment groups were observed in the occurrence of constipation, diarrhoea, or nausea and vomiting (Frick, M. H., Elo, O., Haapa, K. et al 1987).

### 7.4.3 Cost effectiveness of fibrates

There were no cost effectiveness studies found on the use of fibrates compared with placebo in the prevention of CVD.

### 7.4.4 Evidence to recommendations - fibrates

The GDG considered that there was insufficient evidence to routinely recommend the use of fibrates as a first line treatment for the primary prevention of CVD. It was decided, however, that they may be offered as an alternative for those who are intolerant of statin therapy.

### 7.5 Nicotinic acids

#### 7.5.1 Evidence statements for nicotinic acids

| 7.5.1.1 | No randomised controlled trials were identified that compared nicotinic acid therapy with placebo in people at high risk of CVD. |

#### 7.5.2 Clinical effectiveness of nicotinic acids

No randomised controlled trials were identified that compared nicotinic acid therapy with placebo in people at high risk of CVD.
7.5.3 Cost effectiveness of nicotinic acids

There were no cost effectiveness studies found on the use of nicotinic acids compared with placebo in the prevention of CVD.

7.6 Anion exchange resins

7.6.1 Evidence statements for anion exchange resins

One randomised controlled trial in men with elevated total and LDL cholesterol found that cholestyramine therapy was associated with a reduction in the incidence of the combination of CHD death and nonfatal MI but did not confer any benefit for the individual components of this outcome compared with placebo. Cholestyramine therapy was not associated with a reduction in all cause mortality compared with placebo.

7.6.2 Clinical effectiveness of anion exchange resins

One randomised controlled trial, the Lipid Research Clinics Coronary Primary Prevention Trial was identified that compared anion exchange resin therapy with placebo in people at high risk of CVD (1984); (Lipid Research Clinics Coronary Primary Prevention Trial. 1984).

This trial recruited men aged 35-59 years with a total cholesterol level of \( \geq 6.88 \) mmol/l and an LDL cholesterol level of \( \geq 4.92 \) mmol/l. A total of 3,806 men were randomised to receive either cholestyramine (24 g per day) or placebo. During a pre-randomisation phase, all participants received dietary advice which aimed to decrease total cholesterol levels by 3-5%. Participants were then followed up for a mean duration of 7.4 years (1984); (Lipid Research Clinics Coronary Primary Prevention Trial. 1984).

Cholestyramine therapy was associated with a reduction in the primary endpoint of a combination of CHD death and nonfatal MI (reduction in risk 19%, 90% CI 3% to 32%, \( P < 0.05 \)). Cholestyramine therapy did not confer any benefit compared with
placebo for the individual components of this endpoint or for the outcome of all cause mortality.

Cholestyramine therapy was associated with a reduction in the secondary outcomes of development of angina ($P < 0.01$) and the development of a new positive exercise test result ($P < 0.001$) but did not confer any benefit compared with placebo for the outcomes of coronary bypass surgery or peripheral vascular disease.

Gastrointestinal side effects occurred more frequently in the group that received cholestyramine compared with those allocated placebo after 1 year (43% reported at least one gastrointestinal side effect in the placebo group versus 68% in the cholestyramine group). After seven years, incidence of side effects was similar between groups. There were no differences in the incidence of non gastrointestinal side effects between the groups (1984);(Lipid Research Clinics Coronary Primary Prevention Trial. 1984).

7.6.3 Cost effectiveness of anion exchange resins

There were no cost effectiveness studies found on the use of anion exchange resins compared with placebo in the prevention of CVD.

7.6.4 Evidence to recommendations – anion exchange resins

The GDG considered that there was insufficient evidence to routinely recommend the use of anion exchange resins as a first line treatment for the primary prevention of CVD. It was decided, however, that they may be offered as an alternative for those who are intolerant of statin therapy.
7.7 Ezetimibe

7.7.1 Evidence statements for ezetimibe

Please refer to NICE Technology Appraisal No. XX ‘Ezetimibe for the treatment of primary (heterozygous familial and non-familial) hypercholesterolaemia’, (National Institute for Health and Clinical Excellence. 2007)

7.7.2 Clinical effectiveness of ezetimibe

The NICE Technology Appraisal XX entitled ‘Ezetimibe for the treatment of primary (heterozygous familial and non-familial) hypercholesterolaemia’, (National Institute for Health and Clinical Excellence. 2007) is currently being developed. The draft guidance recommends ezetimibe as a treatment option for primary (heterozygous familial and non-familial) hypercholesterolaemia and states that its recommendations should be read in the context of the lipid modification clinical guideline (this guidance).

The population groups covered by the ezetimibe Technology Appraisal XX (National Institute for Health and Clinical Excellence. 2007) are:

- Adults with primary (heterozygous familial and non-familial) hypercholesterolaemia who are candidates for treatment with statins on the basis of their CVD status or risk and;
- whose condition is not appropriately controlled with a statin alone or;
- in whom a statin is considered inappropriate or is not tolerated.

The term “not appropriately controlled with a statin alone” is defined as failure to achieve a target lipid level that is appropriate for a particular group or individual. It also assumes that statin therapy is optimised.

The NICE Technology Appraisal XX (National Institute for Health and Clinical Excellence. 2007) ‘Ezetimibe for the treatment of primary (heterozygous familial and non-familial) hypercholesterolaemia’ did not identify any randomised controlled trials.
that reported health-related quality of life or clinical endpoints such as cardiovascular morbidity and mortality; in the trials identified, surrogate outcomes such as total cholesterol, LDL cholesterol, HDL cholesterol and triglyceride levels were used as indicators of clinical outcomes.

To represent the population of people with hypercholesterolaemia that is not appropriately controlled with statin therapy, six 12-week fixed-dose randomised controlled trials (n = 3610) were identified that compared ezetimibe plus statin therapy with statin therapy alone.

Seven randomised controlled trials (n = 2577) comparing ezetimibe monotherapy with placebo represented the population where statin therapy is considered inappropriate or is not tolerated. All were 12-week studies and were included in a meta-analysis performed by the Assessment Group.

All trials involved people with primary hypercholesterolaemia with average baseline LDL cholesterol levels ranging from 3.4 mmol/litre to 6.5 mmol/litre and included mixed populations of people with and without a history of CVD.

### 7.7.3 Cost effectiveness of ezetimibe

The results of the cost effectiveness analysis carried out by the NICE Technology Appraisal (National Institute for Health and Clinical Excellence, 2007) will be adopted by this guideline.

### 7.7.4 Evidence to recommendations - ezetimibe

Final recommendations of the NICE Technology Appraisal entitled ‘Ezetimibe for the treatment of primary (heterozygous familial and non-familial) hypercholesterolaemia’ will be adopted by this guideline.
7.8 Combination drug therapy

7.8.1 Evidence statements for combination drug therapy

7.8.1.1 No randomised controlled trials with cardiovascular outcomes were identified that compared adding a fibrate, anion exchange resin, or nicotinic acid to a statin with statin monotherapy in people at high risk of CVD.

A systematic review of cohort studies, randomised trials, voluntary notifications to regulatory authorities and published case reports found the incidence of rhabdomyolysis to be ten fold higher when a statin was combined with the fibrate gemfibrozil.

7.8.2 Evidence to recommendations – combination drug therapy

The GDG considered that there was insufficient evidence to recommend combining a statin with a fibrate, anion exchange resin, nicotinic acid or ezetimibe in primary prevention. In addition, it was noted that the combination of a statin with a fibrate may be associated with an increased risk of adverse events.
8 Lifestyle modifications for the secondary prevention of cardiovascular disease (CVD)

8.1 Recommendations for lifestyle

8.1.1 Cardioprotective dietary advice

8.1.1.1 People with CVD should be advised to eat a diet in which total fat intake is 30% or less of total energy intake, saturated fats are 10% or less of total energy intake, intake of dietary cholesterol is less than 300 mg/day and saturated fats are replaced by increasing the intake of monounsaturated fats. Reference can be made to the Food Standards Agency website which gives further practical advice (www.eatwell.gov.uk/healthydiet/).

8.1.1.2 People with CVD should be advised to eat at least 5 portions per day of fruit and vegetables in line with national guidance for the general population. Examples of what constitutes a portion can be found on the Food Standards Agency website (www.eatwell.gov.uk/healthydiet/).

8.1.1.3 People with CVD should be advised to consume at least two portions of oily fish per week. Please see appendix G for a table of the oil content of fish. The Food Standards Agency website gives further information and advice on healthy cooking methods (www.eatwell.gov.uk/healthydiet/).

8.1.1.4 Omega 3 fatty acid supplements should not routinely be recommended for the reduction of cardiovascular risk in patients with angina, peripheral arterial disease or stroke.

8.1.2 Plant stanols and sterols recommendations

8.1.2.1 Plant sterols and stanols should not be routinely recommended for the reduction of risk of CVD.

8.1.3 Physical activity recommendations
### 8.1.3.1 People with CVD should be advised to take 30 minutes of at least moderate intensity physical activity a day, at least five days a week in line with national guidance for the general population (see the Chief Medical Officer's 2004 report at [www.dh.gov.uk](http://www.dh.gov.uk)).

### 8.1.3.2 People who are unable to perform moderate intensity exercise at least five days a week because of comorbidity, medical conditions or personal circumstances should be encouraged to exercise at their maximum safe capacity.

### 8.1.3.3 Recommended types of activity include those that can be incorporated into everyday life such as brisk walking, using stairs and cycling (see the Chief Medical Officer's 2004 report at [www.dh.gov.uk](http://www.dh.gov.uk)).

### 8.1.3.4 People should be advised that shorter bouts of physical activity of 10 minutes or more accumulated throughout the day are as effective as longer sessions of activity (see the Chief Medical Officer's 2004 report at [www.dh.gov.uk](http://www.dh.gov.uk)).

### 8.1.3.5 Advice regarding physical activity should take into account the person's needs, preferences, and circumstances. Goals should be agreed and the person should be provided with written information about the benefits of activity and local opportunities to be active. (For further information, please see NICE public health intervention guidance ‘Four commonly used methods to increase physical activity: brief interventions in primary care, exercise referral schemes, pedometers and community-based exercise programmes for walking and cycling’, PHI002, 2006).

## 8.1.4 Weight management recommendations

### 8.1.4.1 People with CVD who are overweight or obese should be offered appropriate advice and support to achieve and maintain a healthy weight in line with the NICE guideline ‘Obesity: the prevention, identification, assessment and management of overweight and obesity in adults and
8.1.5 Smoking cessation recommendations

8.1.5.1 All patients who smoke should be advised to quit and be offered assistance from a smoking cessation service in line with NICE public health intervention guidance ‘Brief interventions and referral for smoking cessation in primary care and other settings’, PHI001, 2006.

8.1.5.2 All patients who smoke and who have expressed a desire to quit should be offered support and advice, and referral to an intensive support service (for example the NHS Stop Smoking Services) in line with NICE public health intervention guidance 001, ‘Brief interventions and referral for smoking cessation in primary care and other settings’, 2006. Patients who are unable or unwilling to accept a referral they should be offered pharmacotherapy in line with recommendations from the NICE TA ‘Nicotine replacement therapy’ (NRT) and bupropion for smoking cessation’ TA39, 2002.

8.2 Introduction to lifestyle for the secondary prevention of CVD

There is limited trial evidence for the effectiveness of lifestyle interventions on morbidity and mortality in people with established CVD. Most trial evidence relates to patients following a -myocardial infarction and that evidence is covered in the NICE guideline: ‘Myocardial infarction: Secondary prevention in primary and secondary care for patients following a myocardial infarction’, CG48 (2007). Trial literature is almost completely absent for lifestyle interventions in secondary prevention of stroke and peripheral vascular disease.

There is however an extensive literature on the aetiology outcome and management of CVD from patho-physiological data, and from observational, epidemiological, and cohort studies. The 1976 Doll and Peto study on mortality in relation to smoking: 20 years observation of British doctors (Doll, R. and Peto, R. 1976) remains a seminal descriptor of a clearly defined and modifiable risk factor. Although no randomised controlled trials of smoking cessation in patients after a myocardial infarction have been conducted, there is clear evidence from observational studies that smoking
cessation is associated with 40% lower morbidity and mortality (Aberg, A. et al 1983).

The observational literature on diet, dietary modification and physical activity provides a large body of evidence that has been periodically reviewed for major national initiatives. It is beyond the resources of this guideline to attempt such a review, and we have referred to the UK national consensus on these topics and provided references to the national governmental organisations that have made recommendations. Trial literature on dietary modification and physical activity is complex because of the difficulty of establishing accurate and replicable definitions of the activity itself and subsequent changes in it. Where there is trial evidence we have reported this. However, in doing so we are acutely aware that this limited trial evidence may not adequately reflect either the strength or breadth of evidence that can be derived from epidemiology and other observational work.
### 8.3 Cardioprotective dietary advice

#### 8.3.1 Evidence statements for cardioprotective dietary advice

<table>
<thead>
<tr>
<th>Low fat diet</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>8.3.1.1</strong> In patients with suspected CHD, one small randomised controlled trial found that adopting a lipid–lowering diet reduced total cardiac events compared to usual care but did not confer any benefit for the outcomes of cardiovascular mortality, MI, stroke, coronary surgery or angioplasty. Lipid–lowering diet was associated with decreased total and LDL cholesterol compared to baseline levels.</td>
</tr>
<tr>
<td><strong>8.3.1.2</strong> No randomised controlled trials were identified that compared low fat diet with usual diet in patients with peripheral arterial disease or following stroke.</td>
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<tr>
<th>Increased fruit and vegetables diet</th>
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<tr>
<td><strong>8.3.1.3</strong> One randomised controlled trial in patients with angina found that advice to increase consumption of fruit and vegetables was not associated with a reduction in all cause mortality, cardiac death or sudden death compared with advice to eat sensibly.</td>
</tr>
<tr>
<td><strong>8.3.1.4</strong> No randomised controlled trials were identified that compared increased fruit and vegetables diet with usual diet in patients with peripheral arterial disease or following stroke.</td>
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<tr>
<th>Increased omega 3 fatty acids (dietary or supplementation)</th>
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<tr>
<td><strong>8.3.1.5</strong> One randomised controlled trial in patients with angina showed that advice to increase consumption of oily fish or take omega 3 fatty acid supplements as a partial or total substitute was not associated with a reduction in all cause mortality or cardiac death compared with advice to eat sensibly.</td>
</tr>
</tbody>
</table>
Further analysis showed that ‘all fish advice’ (a composite of advice to increase consumption of oily fish or take supplements plus advice to increase consumption of oily fish or take supplements and increase consumption of fruit and vegetables) was associated with an increased risk of sudden death compared with ‘no fish advice’ (a composite of advice to increase consumption of fruit and vegetables plus advice to ‘eat sensibly’).

Subgroup analysis found this excess risk to be restricted to patients sub randomised to receive omega 3 fatty acid supplements during the second phase of the trial who were found to have an increased risk of cardiac death and sudden death compared with those randomised to receive ‘no fish advice’ throughout both phases of the trial.

Three cost effectiveness studies and a further cost effectiveness report done for the MI guideline found that omega-3- acid ethyl esters supplementation compared to no supplementation in patients after MI is cost effective.

8.3.1.6 No randomised controlled trials were identified that compared increased consumption of omega 3 fatty acids with usual diet in patients with peripheral arterial disease or following stroke.

8.3.2 Clinical effectiveness of low fat diets

One randomised controlled trial was identified in patients with a history of CVD that compared advice to adopt a low fat diet with no dietary advice (Watts, G. F. et al 1992). This trial recruited men referred for coronary angioplasty to investigate angina pectoris, or other findings suggestive of coronary heart disease (CHD) (70% with angina, 45% with a history of MI). A total of 90 participants were randomised to one of three groups; usual care, lipid-lowering diet, or lipid-lowering diet plus cholestyramine therapy. Patients in the lipid-lowering diet and lipid-lowering diet plus cholestyramine therapy groups were given the following advice by a dietician: to reduce total fat intake to 27% of dietary energy, to reduce saturated fat intake to 8-10% of dietary energy, to reduce dietary cholesterol to 100 mg / 1000 kcal, to
increase omega 3 and 6 fatty acid intake to 8% of dietary energy, and to increase fibre intake. Participants were followed up for a mean duration of 39 months.

Lipid-lowering diet did not confer any benefit over usual care for the outcomes of cardiovascular death, MI, coronary surgery, angioplasty or stroke. Lipid-lowering diet did, however, reduce total cardiac events compared with usual care (10/28 (36%) lipid-lowering diet versus 3/27 (11%) usual care) ($P < 0.05$) and improve the severity of angina symptoms ($P < 0.01$ lipid-lowering diet versus usual care).

Participants in the lipid-lowering diet group had lower total and LDL cholesterol levels at the end of the trial (39 months) compared with their baseline levels ($P < 0.01$), while there was no change in HDL cholesterol (Watts, G. F., Lewis, B., Brunt, J. N. et al 1992).

### 8.3.3 Evidence into recommendations

This randomised controlled trial recruited small numbers and was the only trial identified in patients with angina, stroke or peripheral arterial disease. The GDG decided to adopt recommendations made in the Joint British Societies' guidelines on prevention of CVD in clinical practice (2005) which recommends that total fat intake should be 30% or less of total energy intake and saturated fats should comprise 10% or less of total energy intake. These targets are slightly lower for total fat than those set by the Department of Health for the general population (total fat $\leq 35\%$ of total energy intake and saturated fats $\leq 10\%$ of total energy intake) (Department of Health 2005)

### 8.3.4 Clinical effectiveness of increased fruit and vegetables diet

One randomised controlled trial was identified in patients with a history of CVD that compared advice to increase fruit and vegetables versus non specific dietary advice (Burr, M. L. et al 2003). This trial recruited men under the age of 70 who were being treated for angina (50% also had a prior MI). Recruitment occurred in two phases: Phase I was between 1990 and 1992 and phase II between 1993 and 1996, follow up was in 1999. A total of 3114 participants were randomised to one of four groups:

1. Advice to eat at least 2 portions of oily fish per week or take up to 3 ‘MaxEPA’ fish oil capsules daily (each capsule contains 170 mg EPA and 115 mg DHA)
as a partial or total substitute. In the first phase of the study, participants
chose diet or capsules or a mixture, in the second phase, participants were
sub randomised to receive dietary advice or fish oil capsules.

2. Advice to eat 4-5 portions of fruit and vegetables, to drink one glass of orange
juice daily and to increase intake of soluble fibre in the form of oats.

3. A combination of 1. and 2.

4. ‘Sensible eating’ – non-specific advice that did not include either of the above
interventions.

Advice to increase consumption of fruit and vegetables was found to be poorly
complied with and the advice did not confer any benefit on mortality (all deaths,
cardiac deaths and sudden deaths) compared with ‘sensible eating’.

8.3.5 Evidence into recommendations
This was the only randomised controlled trial found on the effectiveness of an
increased fruit and vegetables diet in patients with angina and no randomised
controlled trials were identified in patients with peripheral arterial disease or following
stroke. The GDG decided to recommend five portions of fruit and vegetables per
day in line with advice given to the general population. For further information,
please refer to the Department of Health paper ‘Choosing a Better Diet: a food and
health action plan’ (Department of Health 2005), the COMA report ‘Nutritional
Aspects of Cardiovascular Disease’ (de la Hunty, A. 1995) and the food standards
agency website (www.eatwell.gov.uk/healthydiet/) (Food Standards Agency 2007).

8.3.6 Clinical effectiveness of increased omega 3 fatty acids (dietary or
supplementation)
One randomised controlled trial was identified in patients with a history of CVD which
compared increased consumption of oily fish or taking omega 3 fatty acid
supplements versus no change in diet (Burr, M. L., shfield-Watt, P. A., Dunstan, F.
D. et al 2003). This trial has previously been described in section 1.3.4. A total of
3114 participants were randomised to one of four groups:
1. Advice to eat at least 2 portions of oily fish per week or take up to 3 ‘MaxEPA’ fish oil capsules daily (each capsule contains 170 mg EPA and 115 mg DHA) as a partial or total substitute. In the first phase of the study, participants chose diet or capsules or a mixture, in the second phase, participants were sub randomised to receive dietary advice or fish oil capsules.

2. Advice to eat 4-5 portions of fruit and vegetables, to drink one glass of orange juice daily and to increase intake of soluble fibre in the form of oats.

3. A combination of 1. and 2.

4. ‘Sensible eating’ – non-specific advice that did not include either of the above interventions.

Four way analysis found that advice to eat oily fish or take supplements was not associated with a significant change in total number of deaths, number of cardiac deaths or number of sudden deaths compared with the control group who were told to ‘eat sensibly’.

Two way analysis comparing ‘all fish advice’ (intervention groups 1 and 3) with ‘no fish advice’ (intervention group 2 and control group 4) found that advice to eat oily fish or take supplements was not associated with a change in the total number of deaths but was associated with an increase in the number of cardiac deaths (11.5% ‘all fish advice’ versus 9.0% ‘no fish advice’, \( P = 0.02 \)) and number of sudden deaths (4.6% ‘all fish advice’ versus 3% ‘no fish advice’, \( P = 0.02 \)).

Adjusted hazard ratios were calculated for ‘all fish advice’ (intervention groups 1 and 3) compared to ‘no fish advice’ (intervention group 2 and control group 4). ‘All fish advice’ was found to be associated with an increase in the risk of sudden death (HR 1.54, 95% CI 1.06 to 2.23) compared with ‘no fish advice’ but no change was observed for total or cardiac mortality.

A subgroup analysis was performed and adjusted hazard ratios were calculated separately for those given fish advice (intervention groups 1 and 3) who were sub-randomised to receive omega 3 fatty acid supplements (a subset of 462 patients were sub-randomised to this treatment during the second phase of recruitment) and...
all others given ‘fish advice’ who were not sub randomised (n = 1109) compared with ‘no fish advice’ (intervention group 2 and control group 4). It was found that those sub randomised to receive omega 3 fatty acid supplements during the second phase of the trial had an increased risk of cardiac death (HR 1.45, 95% CI 1.05 to 1.99) and sudden death (HR 1.84, 95% CI 1.11 to 3.05) compared with those randomised to receive ‘no fish advice’ throughout the trial. All other participants who received ‘fish advice’ (intervention groups 1 and 3) but were not sub randomised to receive supplements were not found to have an increased risk of total mortality, cardiac mortality or sudden death compared with ‘no fish advice’.

8.3.7 Evidence into recommendations

Due to the conflicting results of this study for oily fish consumption compared with omega 3 fatty acid supplementation and the lack of evidence for patients with peripheral arterial disease or following stroke, the GDG considered that for dietary fish, the recommendations made by the Joint British Societies’ guidelines on prevention of CVD in clinical practice (2005) should be adopted, which recommends at least two servings of omega-3 fatty acid containing fish per week. The GDG decided that there was insufficient evidence to recommend omega 3 fatty acid supplementation in patients with angina, peripheral arterial disease or stroke.
8.3.8 Evidence statements for plant stanols and sterols

8.3.8.1 No randomised controlled trials with cardiovascular endpoints were identified that compared giving plant stanols or sterols with usual diet in patients with CVD.

8.4 Regular physical activity

8.4.1 Evidence statements for regular physical activity

8.4.1.1 No randomised controlled trials were identified in patients with angina, peripheral arterial disease or following stroke that compared regular physical activity with sedentary lifestyle for the outcomes of mortality or morbidity.

8.4.1.2 In selected patients after an MI, randomisation to an exercise prescription programme reduced the risk of death from MI after 3 years, but not all cause or cardiovascular mortality.

8.4.1.3 In selected patients after an MI, exercise performed at a level sufficient to increase physical work reduced all cause mortality and cardiovascular mortality in long term follow up.

8.4.1.4 One small randomised controlled trial in patients with stable intermittent claudication showed that physical training classes were not associated with a reduction in total cholesterol or triglyceride levels compared with usual care.

8.4.1.5 Two cost effectiveness studies concluded that exercise programmes are cost effective compared to no exercise programme in patients with CHD.

8.4.2 Clinical effectiveness of regular physical activity

No randomised controlled trials were identified in patients with a history of angina alone, stroke, or peripheral arterial disease that examined the effect of regular
physical activity versus a sedentary lifestyle for the outcomes of all cause mortality,
cardiovascular mortality or cardiovascular morbidity.

One randomised controlled trial was identified on the effectiveness of regular
physical activity versus sedentary lifestyle to modify lipid profiles in patients with a
history of stable intermittent claudication for at least six months (Gelin, J. et al
2001). The trial recruited men and women from a regional cohort of 400 to 500
people. A total of 264 participants were randomised to one of three groups:

1. Usual care
2. Physical training classes (a program of 3 X 30 minute sessions of specific
   walking training per week for the first six months, supervised by a
   physiotherapist. From 6 months to 1 year, 2 sessions per week were offered)
3. Invasive treatment (endovascular or open surgical procedure).

Participants were then followed up for 1 year. Physical training classes did not
confer any benefit over usual care for the primary outcome of maximum exercise
power in Watts or for the secondary physiological endpoints. Total cholesterol and
triglycerides were measured at randomisation and at 1 year and there were no
differences between the physical training class and usual care groups. In addition,
no difference in the number of deaths was seen between groups however, this was
not a pre-specified outcome measure.

Due to the lack of clinical outcome data in this trial, it was decided by the GDG to
consider evidence used in the NICE guidance: ‘Myocardial infarction: Secondary
prevention in primary and secondary care for patients following a myocardial
infarction’, CG48 (2007)

Two studies were identified which examined the impact of regular physical activity to
improve outcome in patients with a prior MI. The first study was a randomised
controlled trial in 651 men, aged 35 to 64 years with a documented MI greater than
or equal to 8 weeks but less than 3 years before recruitment conducted between
The exercise intervention was an individualised exercise prescription based on the patient’s ECG-monitored treadmill multistage graded test (MSET). An exercise target heart rate guided the prescription and was determined as 85% of the peak rate achieved on the MSET. This group performed brisk physical activity in the laboratory for 8 weeks (1 hour per day, 3 times per week). After 8 weeks, participants exercised in a gymnasium or swimming pool (15 minutes cardiac exercise followed by 25 minutes of recreational games). Participants were encouraged to attend 3 sessions per week. Patients in the control group were told to maintain their normal routine but not to participate in any regular exercise.

At the 3 year follow up, randomisation to the exercise prescription programme was found to be associated with a reduction in death from MI (RR 0.13, 95% CI 0.02 to 0.78) compared with control. The exercise intervention was not associated with a reduction in all cause mortality (RR 0.63, 95% CI 0.32 to 1.15) or cardiovascular mortality (RR 0.71, 95% CI 0.34 to 1.33) compared with control. The authors noted that by the end of the trial 23% of the treatment group had stopped attending exercise sessions, whereas 31% of the control group reported that they were exercising regularly (Naughton, J., Dorn, J., and Imamura, D. 2000). A secondary analysis of this data (Dorn, J. et al. 1999) presented age-adjusted risk ratios and it was found that at the 3 year follow up point, the exercise intervention was associated with a reduction in all cause mortality (0.86, 95% CI 0.76 to 0.98) but not CVD mortality (0.87, 95% CI 0.74 to 1.02) compared with control.

After 3 years of the trial, the patients were followed up for 5, 10, 15 and 19 years examining all cause mortality and cardiovascular mortality. The results of this follow-up were published in the second study (Dorn, J., Naughton, J., Imamura, D. et al. 1999) which was a secondary analysis of the first study. For long term follow up at 5, 10, 15 and 19 years, the age adjusted relative risk reductions for all cause mortality were 0.91 (95% CI 0.82 to 1.00), 0.88 (95% CI 0.83 to 0.95), 0.89 (95% CI 0.84 to 0.95) and 0.92 (95% CI 0.87 to 0.97), respectively for the exercise prescription programme compared with control. For long term follow up at 5, 10, 15 and 19 years, the age adjusted relative risk reductions for CVD mortality were 0.91 (95% CI 0.81 to 1.03), 0.89 (95% CI 0.82 to 0.96), 0.89 (95% CI 0.82 to 0.96) and
0.93 (95% CI 0.87 to 0.99), respectively for the exercise prescription programme compared with control.

Thus, improvement in physical work capacity resulted in consistent survival benefits throughout the full 19 years. The authors concluded that exercise performed at a level sufficient to increase physical work capacity may have long-term survival benefits in MI survivors.

8.4.3 Evidence into recommendations

It was decided by the GDG that recommendations would be made based on those of the Chief Medical Officer's report 'At least five a week: Evidence on the impact of physical activity and its relationship to health' (Chief Medical Officer 2004) and the NICE public health intervention guidance no. 2 'Four commonly used methods to increase physical activity: brief interventions in primary care, exercise referral schemes, pedometers and community-based exercise programmes for walking and cycling' (National Institute for Health and Clinical Excellence 2007) and the Joint British societies' guidelines on prevention of CVD in clinical practice (2005).

Please refer to chapter 5 (lifestyle for the primary prevention of CVD) for further details of the Chief Medical Officer's report and see the full report at www.dh.gov.uk.

8.4.4 Cost effectiveness of regular physical activity

For cost effectiveness discussion of regular physical activity, see section 5.5.4 in the primary prevention lifestyle chapter.

8.5 Weight management

For guidance in weight management in patients with CVD refer to the NICE guideline:

8.6 Smoking cessation

For guidance on smoking cessation refer to the NICE Technology appraisal:

- Smoking cessation - bupropion and nicotine replacement therapy. The clinical effectiveness and cost effectiveness of bupropion (Zyban) and Nicotine Replacement Therapy for smoking cessation TA039 (2002).

And also the NICE Public health intervention guidance:

- Brief interventions and referral for smoking cessation in primary care and other settings PHI001, (2006).
9 Drug therapy for the secondary prevention of cardiovascular disease (CVD)

9.1 Recommendations for drug therapy

9.1.1 Overall drug therapy recommendation

9.1.1.1 When considering therapy for lipid modification, all modifiable cardiovascular risk factors should be considered and their management optimised. Assessment should include evaluation of:

- smoking status
- blood pressure
- body mass index or other measure of obesity (refer to NICE Obesity guideline, No. CG43, 2006).
- fasting total cholesterol, LDL cholesterol, HDL cholesterol and triglycerides
- fasting blood glucose
- renal function
- liver function (transaminases).

Secondary causes of dyslipidaemia should be considered and excluded before starting lipid therapy. This should include measurement of thyroid stimulating hormone (TSH).

9.1.2 Statin recommendations

9.1.2.1 Statin therapy is recommended for adults with clinical evidence of CVD (NICE technology appraisal 94, ‘Statins for the prevention of cardiovascular events’ 2007).
9.1.2.2  When the decision has been made to prescribe a statin, it is recommended that therapy should usually be initiated with a drug with a low acquisition cost (taking into account required daily dose and product price per dose) (NICE technology appraisal 94, 'Statins for the prevention of cardiovascular events' 2007).

9.1.2.3  The decision whether to initiate statin therapy should be made after an informed discussion between the responsible clinician and the individual about the risks and benefits of statin treatment, taking into account additional factors such as comorbidities and life expectancy.

9.1.2.4  Treatment should be initiated with simvastatin 40 mg for patients in the following groups:

- after myocardial infarction, or acute coronary syndrome or new onset angina
- with chronic stable angina
- after ischaemic stroke or transient ischaemic episode
- with peripheral arterial disease.

Where there are drug interactions or simvastatin 40 mg is contraindicated, a lower dose or alternative preparation may be chosen.

9.1.2.5  A target for total cholesterol or LDL cholesterol is not recommended for people with established CVD who are treated with a statin. Statins should be up-titrated if the patient does not reach a total cholesterol of 4 mmol/l or LDL cholesterol 2mmol/l on the initial dose. This decision should be made after considering the benefits and risks of treatment and informed patient preferences.

Clinical judgement should be used for people who have comorbidities that may make such increases in treatment inappropriate, or in people receiving multiple drug therapy that may increase the risk of adverse reactions.

9.1.2.6  A fixed percentage reduction in total or LDL cholesterol is not recommended for
individuals with established CVD who are treated with a statin.

9.1.2.7 An 'audit' level of total cholesterol of 5 mmol/l can be used to assess progress in populations or groups of people with CVD.

9.1.2.8 Routine monitoring of creatine kinase is not recommended in asymptomatic patients who are being treated with a statin.

9.1.2.9 People who are being treated with a statin should be advised to seek medical advice if they develop muscle symptoms (pain, tenderness or weakness). If this occurs creatine kinase should be measured.

9.1.2.10 Any statin may need to have the dose reduced or be temporarily or permanently stopped if other drugs are introduced or treatment is required for a concomitant illness that interferes with metabolic pathways or increases the propensity for drug and food interactions.

9.1.2.11 Baseline liver enzymes should be measured before starting a statin. Liver function enzymes should be measured within 6 months of starting treatment and again at 12 months but not again unless clinically indicated.

9.1.2.12 People who have raised liver enzymes (transaminases) should not routinely be excluded from statin therapy.

9.1.2.13 Statins should be discontinued in people who develop an unexplained peripheral neuropathy and further advice from a specialist should be sought.

1 9.1.3 Fibrates recommendations

9.1.3.1 Fibrates may be considered in people with CVD who are intolerant of statins.

2 9.1.4 Nicotinic acid recommendations

9.1.4.1 Nicotinic acids may be considered in people with CVD who are intolerant of statins.
9.1.5 **Anion exchange resins recommendations**

9.1.5.1 Anion exchange resins may be considered in people with CVD who are intolerant of statins.

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9.1.6 **Ezetimibe recommendations**

9.1.6.1 Please refer to NICE Technology Appraisal No. XX ‘Ezetimibe for the treatment of primary (heterozygous familial and non-familial) hypercholesterolaemia’, (National Institute for Health and Clinical Excellence. 2007)

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9.1.7 **Lipid measurement recommendations**

9.1.7.1 Before commencing lipid modifying treatment, people should have at least two pre-treatment readings taken, one of which should be a fasting lipid sample measuring total cholesterol, LDL cholesterol, HDL cholesterol and triglycerides. An exception may be made regarding the need for a fasting lipid sample if a random triglyceride level is already known to be 2 mmol/l or less.

9.1.7.2 Where a statin is started after an acute event, it is appropriate to measure a fasting lipid sample at around 3 months and statin treatment should not be delayed.

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9.2 **Introduction to drug therapy for secondary prevention**

9.2.1.1 **The effectiveness of lipid modifying drugs**

The GDG based recommendations to use lipid modifying drugs on trial evidence of improvement in cardiovascular outcomes and where available, total mortality. For people with established CVD there is substantive trial evidence that statins reduce total mortality, cardiovascular mortality and morbidity and total mortality and are cost-effective. This evidence is strongest for people with coronary heart disease (CHD) (Baigent, C., Keech, A., Kearney, P. M. et al 2005); (National Institute for Health and Clinical Excellence 2006).
Among people with CHD treated with statins there is a reduction in recurrent CHD events of about 23%, (rate ratio (RR) 95% CI 0.74 to 0.80) and a reduction in stroke events by 17% (0.78 to 0.88) (Baigent, C., Keech, A., Kearney, P. M. et al 2005).

For people with stroke there is a reduction in stroke and cardiovascular events using higher intensity statins (Amarenco, P. et al 2003).

Although there have been no statin trials specifically in people with peripheral arterial disease (PAD), the Heart Protection Study demonstrated the benefits of statin therapy in patients with PAD. Allocation to simvastatin 40mg daily reduced the rate of first major vascular events by about one-quarter, and that of peripheral vascular events by about one-sixth, with large absolute benefits seen in participants with PAD because of their high vascular risk (Heart Protection Study Collaborative Group. 2007).

Fibrates have been shown to reduce some cardiovascular events in people with CHD though in comparison to statins their lower efficacy and adverse event profile has meant that statins are the drug of first choice for most people. Nicotinic acid and anion-exchange resins have also shown evidence of cardiovascular benefit.

The NICE Statin Technology Appraisal ‘Statins for the prevention of cardiovascular events’ 2006 has thoroughly and comprehensively reviewed the evidence on the effectiveness and cost effectiveness of statins and our recommendations on the initiation of statin therapy are based upon this report states that:

- Statin therapy is recommended for adults with clinical evidence of CVD
- The decision to initiate statin therapy should be made after an informed discussion between the responsible clinician and the individual about the risks and benefits of statin treatment, and taking into account additional factors such as comorbidity and life expectancy
- When the decision has been made to prescribe a statin, it is recommended that therapy should be initiated with a drug with a low acquisition cost (taking into account required daily dose and product price per dose).
9.2.1.2 The association between lipid modification using drugs and cardiovascular events

The epidemiological relationship between cholesterol as a risk factor in populations and groups and cardiovascular events is well established. As cholesterol increases, so does the risk of CVD. This relationship is such that each 1mmol/l rise in total cholesterol is associated with a 72% increase in the risk of a major coronary event (Emerson, J. R., Whincup, P. H., Morris, R. W. et al 2003).

There is now compelling randomised controlled trial evidence in people with established CVD, that lowering cholesterol with statins reduces total mortality, cardiovascular mortality and morbidity. For the statin class at lower and moderate intensity each 1mmol/l reduction in LDL cholesterol will produce a proportional reduction in major vascular events of 23% (at least down to an LDL cholesterol of 2 mmol/l) (Baigent, C., Keech, A., Kearney, P. M. et al 2005).

Statins are highly cost-effective with a good record of safety. There is also good evidence that higher intensity statins are associated with additional cost-effective reductions in cardiovascular events for people after recent myocardial infarction and acute coronary syndrome.

However the benefits of cholesterol lowering and safety cannot be assumed for all drug classes or for all drugs within the same class (Psaty, B. M., Weiss, N. S., Furberg, C. D. et al 1999) and cardiovascular outcome and adverse event data should be available for every drug from clinical trials. The withdrawal of the statin cerivastatin because of adverse events is a salutary reminder that all drugs within a class are not the same and that there may be specific drug effects within a drug class.

The same strength of evidence that exists for statins does not exist for other classes of lipid lowering drugs (fibrates, anion exchange resins, nicotinic acid) where the trials are fewer in number, the total patient population studied is smaller, and trials have shown variable benefits on cardiovascular events but no reduction in total mortality despite reduction in cholesterol.

Other classes of drug have either failed to improve cardiovascular outcomes or even increased mortality. Torcetrapib, one of a new class of lipid modifying drug therapies
(CETP inhibitor) which raises HDL cholesterol, was being evaluated in a clinical trial which was stopped prematurely because of excess mortality (Jensen, G. B. and Hampton, J. 2007) (Nissen, S. E. et al 2007).

The potential advantages of drug combinations from different classes cannot be assumed as there are no cardiovascular outcome data for any drug combination in lipid management. There is a greater propensity for major adverse events when statins are combined with fibrates or other drugs particularly when statins are used at higher doses.

9.2.1.3 The use of statins in clinical practice

In the period 1981-2000, CHD mortality under age 84 years in England and Wales fell by 54%; 68 230 fewer deaths. Modelling of the effects of changes in the three major risk factors, smoking, blood pressure and serum cholesterol suggests that these changes are associated with 45 370 fewer deaths. The biggest single contribution to reduction in mortality was estimated to be a decrease in smoking. Approximately 2135 fewer deaths were attributed to statin treatment: 1990 in CHD patients and 145 in people without established disease (Unal, B., Critchley, J. A., and Capewell, S. 2005).

Prescription of statins and other drugs to improve risk factors remains suboptimal despite the fact that half the survivors of hospital admission for acute MI or angina experience a further major coronary event or death within 5 years of discharge (Capewell, S., Unal, B., Critchley, J. A. et al 2006).

Statin prescription has increased dramatically in the last 10 years particularly for people with established CVD. In 1997 Brady et al reported 18% of people with CHD in primary care were on statins (Brady, A. J., Oliver, M. A., and Pittard, J. B. 2001). In 2006, among 150 general practices in East London, statin prescription for people with CHD was 81% (Report: East London Clinical Effectiveness Group Queen Mary University of London 2007).

There is still considerable variation in prescribing and under-dosing by practice and evidence of inequity in prescribing by age and also by sex. Statins are less likely to
be prescribed to people over 75 years and women (de Lusignan, S. et al 2006);(DeWilde, S. et al 2003).

Patient adherence to treatment with statins remains a major challenge and only half the patients at highest risk after myocardial infarction continue to take their statins at 2 years (Penning-van Beest, F. J. et al 2007);(Wei, L. et al 2005).
## 9.3 Statins

### 9.3.1 Evidence statements for statins

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<th>Evidence statements for statins</th>
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<tr>
<td><strong>NICE Technology Appraisal evidence statement for statins</strong></td>
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<tr>
<td>9.3.1.1 In a meta-analysis of 14 randomised controlled trials of secondary prevention in CHD, statin therapy was associated with a reduction in all-cause mortality, CVD mortality, CHD mortality, fatal MI, and coronary revascularisation compared with placebo. (NICE technology appraisal 94, ‘Statins for the prevention of cardiovascular events’ 2007).</td>
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<th>Evidence statements for higher intensity statin therapy</th>
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<td>9.3.1.2 Meta-analysis of four randomised controlled trials in patients with CHD found that higher intensity statin therapy compared with lower intensity statin therapy was associated with a reduction in the composite outcome of coronary death or MI, and with a reduction in the composite outcome of coronary death or any cardiovascular event (MI, stroke, hospitalization for unstable angina or any revascularisation). Higher intensity statin therapy was not associated with a reduction in all cause mortality or cardiovascular mortality compared with lower intensity statin therapy.</td>
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| 9.3.1.3 No randomised controlled trials were identified that compared higher intensity statin therapy with lower intensity statin therapy in patients with peripheral arterial disease or following stroke. |

| 9.3.1.4 One randomised controlled trial in patients following stroke or transient ischaemic attack found that higher intensity |

statin therapy with atorvastatin 80 mg was associated with a reduction in fatal stroke and the composite of fatal and non-fatal stroke compared with placebo. Post-hoc analysis found this beneficial effect to be restricted to patients after ischaemic stroke whereas a harmful effect was found for those patients after hemorrhagic stroke.

Higher intensity statin therapy did not confer any benefit over placebo for the outcome of non-fatal stroke compared with placebo.

Higher intensity statin therapy compared to placebo was found to be cost effective in a model done for the guideline and one published paper.

**Adverse events associated with higher intensity statin therapy**
9.3.1.5 Four randomised controlled trials in patients with CHD found that higher intensity statin therapy was associated with a greater persistent elevation in alanine aminotransferase and/or aspartate aminotransferase levels compared with lower intensity therapy. This was not found to be associated with a significant increase in clinical liver disease.

Three of the four trials found higher intensity statin therapy was not associated with an increase in myalgia compared with lower intensity therapy and one found an excess of myalgia but no increase in the incidence of myopathy.

Three of the four trials found that higher intensity statin therapy was not associated with an increase in rhabdomyolysis compared with lower intensity therapy and one found an excess of rhabdomyolysis in the higher intensity group which was found to be associated with identifiable secondary causes.

9.3.1.6 A retrospective analysis of pooled data from 49 clinical trials found higher intensity statin therapy with atorvastatin 80 mg to be associated with a greater incidence of persistent elevations in alanine aminotransferase and/or aspartate aminotransferase > 3 x ULN compared to standard intensity therapy with atorvastatin 10 mg or placebo.

No incidences of myopathy or rhabdomyolysis were reported and serious hepatic adverse events were rare although a small number of patients receiving high intensity statin therapy developed hepatitis which resolved after discontinuation of drug therapy.

1 9.3.2 Clinical effectiveness of statins
Throughout the guideline, we have reported 95% confidence intervals for relative risks (RR) and odds ratios (OR). Where the 95% confidence interval crosses the ‘line of no effect’ i.e., when the confidence intervals included 1, we have interpreted this as being non-significant. This interpretation holds even when the upper or lower limit of the confidence interval is 1.00.

The NICE Technology Appraisal 94 (NICE technology appraisal guidance 94, ‘Statins for the prevention of cardiovascular events’ 2006) states that:

- Statin therapy is recommended for adults with clinical evidence of CVD.

The recommendation was based on the meta-analysis of 14 randomised controlled trials of secondary prevention in CHD. Of these, four were conducted in MI and/or angina patients (Liem, A. H. et al 2002);(Pedersen, T. R. et al 2004);(Sacks, F. M. et al 2000) (1998). Four studies recruited patients with CAD (Crouse, J. R. et al 1995);(Jukema, J. W. et al 1995);(Pitt, B. et al 1995);(Teo, K. K. et al 2000) two studies recruited patients with CAD and hypercholesterolaemia (Bestehorn, H. P. et al 1997);(Riegger, G. et al 1999) one study recruited patients with mild CAD (1994), two studies enrolled patients after coronary balloon angioplasty (Serruys, P. W. et al 1999) and (Bertrand, M. E. et al 1997), and one study enrolled patients after percutaneous coronary intervention (Serruys, P. W. et al 2002). Statin therapy was associated with a reduction in the following clinical outcomes compared with placebo: all-cause mortality (RR 0.79, 95% CI 0.70 to 0.90), CVD mortality (RR 0.75, 95% CI 0.68 to 0.83), CHD mortality (RR 0.72, 95% CI 0.64 to 0.80), fatal MI (RR 0.57, 95% CI 0.45 to 0.72), unstable angina (RR 0.82, 95% CI 0.72 to 0.94), hospitalisation for unstable angina (RR 0.90, 95% CI 0.70 to 0.90), nonfatal stroke (RR 0.75, 95% CI 0.59 to 0.95), new or worse intermittent claudication (RR 0.64, 95% CI 0.46 to 0.91) and coronary revascularisation (RR 0.77, 95% CI 0.69 to 0.85).

The NICE Technology Appraisal 94 (NICE technology appraisal guidance 94, Statins for the prevention of cardiovascular events’ 2006) further states that:

- The decision to initiate statin therapy should be made after an informed discussion between the responsible clinician and the individual about the risks and benefits of statin treatment, and taking into account additional factors such as comorbidity and life expectancy.
When the decision has been made to prescribe a statin, it is recommended that therapy should be initiated with a drug with a low acquisition cost (taking into account required daily dose and product price per dose).

9.3.3 Clinical effectiveness of higher intensity versus lower intensity statin therapy

No randomised controlled trials were identified that compared higher intensity statin therapy with lower intensity therapy in patients with angina alone, stroke or peripheral arterial disease. In addition, no randomised controlled trials were identified on the effectiveness of up-titrating statin dose compared with giving a fixed dose.

Three randomised controlled trials compared higher intensity statin therapy with lower intensity statin therapy in patients with coronary heart disease: one in patients after acute coronary syndrome (PROVE-IT-TIMI-22) (Cannon, C. P. et al 2004), one in patients with previous myocardial infarction (IDEAL) (Pedersen, T. R. et al 2005) and one which included previous myocardial infarction 58% and/or angina/revascularization (TNT) (LaRosa, J. C. et al 2005)). None of these trials treated to a pre-specified target total or LDL cholesterol, although the achieved levels were lower in each of the higher intensity statin groups, compared with the respective lower intensity statin groups. A fourth trial in patients after acute coronary syndrome, compared early intensive statin therapy with delayed conservative statin therapy (A to Z) (de Lemos, J. A. et al 2004).

The first randomised controlled trial (Cannon, C. P., Braunwald, E., McCabe, C. H. et al 2004) recruited patients within 10 days of an acute coronary syndrome event (29% had unstable angina, 36% non-ST elevation MI and 35% ST elevation MI). A high proportion of trial participants were taking other secondary prevention drugs and over two thirds were revascularised for treatment of the index event. At recruitment patients had to have a total cholesterol of 6.21 mmol/l or less. Patients were randomised to receive either higher intensity statin therapy with atorvastatin (80 mg once daily) or lower intensity statin therapy with pravastatin (40 mg once daily). Lipid values at the start of the study were similar in both groups. At follow up, patients in the atorvastatin group achieved lower levels of LDL cholesterol compared with the
pravastatin group (1.60 mmol/l versus 2.46 mmol/l) and patients in the pravastatin
group achieved higher HDL cholesterol levels.

During a mean follow up of 24 months, there was a reduction in the primary outcome
(a composite of death from any cause, MI, documented unstable angina requiring
rehospitalisation, revascularisation or stroke) with higher intensity therapy compared
with lower intensity (HR 0.84, 95% CI 0.74 to 0.95). Similarly, higher intensity
therapy was associated with a risk reduction of 14% ($P = 0.029$) for the secondary
outcome of a composite of death from coronary heart disease, nonfatal MI or
revascularisation. There was no significant reduction in death from any cause or
reinfarction with higher intensity therapy compared with lower intensity (Cannon, C.

The second study was an open labeled randomised trial in patients with prior MI
(median time since last MI was 22 months) (Pedersen, T. R., Faergeman, O.,
Kastelein, J. J. et al 2005). Most trial participants were taking aspirin and beta
blockers, but almost 2/3 were not taking ACE inhibitors or ARBs. Patients were
assigned to higher intensity atorvastatin 80 mg once daily or lower intensity
simvastatin (20 mg once daily). Further drug titration could be undertaken at 24
weeks within the study protocol, based on achieved total cholesterol levels. Twenty
one percent of patients in the simvastatin group had their dose increased to 40 mg
daily, and 6% of patients in the atorvastatin group had their dose reduced to 40 mg
daily. At the end of the study, 23% were treated with simvastatin 40mg daily and
13% with atorvastatin 40mg daily. During treatment, patients in the atorvastatin
group had lower levels of LDL cholesterol, total cholesterol, triglycerides and
apolipoprotein B compared with the simvastatin group. HDL cholesterol and
apolipoprotein A1 levels were higher in the simvastatin group compared with the
atorvastatin group. Mean LDL cholesterol levels were 2.7 mmol/l in the simvastatin
group and 2.1 mmol/l in the atorvastatin group.

For the primary endpoint of major coronary event (defined as coronary death,
hospitalisation for nonfatal acute MI, or cardiac arrest with resuscitation) there was
no difference in event rates between the two treatment groups during a median
follow up of 4.8 years. There was a reduction in the nonfatal MI component of this
primary endpoint with atorvastatin therapy compared with simvastatin treatment (HR
0.83, 95% CI 0.71 to 0.98). Atorvastatin treatment was associated with a reduction in the secondary endpoint of any CHD event (HR 0.84, 95% CI 0.76 to 0.91) and also a reduction in any major cardiovascular event (HR 0.87, 95% CI 0.78 to 0.98) compared with simvastatin treatment. There were no differences in cardiovascular or all cause mortality (Pedersen, T. R., Faergeman, O., Kastelein, J. J. et al 2005).

The third randomised controlled trial recruited patients with clinically evident stable CHD (59% had a prior MI, 82% angina) (LaRosa, J. C., Grundy, S. M., Waters, D. D. et al 2005). To ensure that, at baseline, all patients had LDL cholesterol levels consistent with the then current guidelines for the treatment of stable CHD, patients with LDL cholesterol levels between 3.4 and 6.5 mmol/l entered an eight week run in period of open-label treatment with 10 mg of atorvastatin per day. At the end of the run in phase, those patients with a mean LDL cholesterol of less than 3.4 mmol/l were randomised. Patients were assigned to either higher intensity atorvastatin (80 mg once daily) or lower intensity atorvastatin (10 mg once daily). The trial follow up was for a median of 4.9 years. No information was given on concomitant medications at baseline or during the trial but it was stated that medication usage was similar in the two groups at the start of the trial. Mean LDL cholesterol levels during the study were 2.0 mmol/l in the group treated with atorvastatin 80 mg once daily and 2.6 mmol/l in the group treated with atorvastatin 10 mg once daily. There was a 22% reduction (95% CI 11% to 31%) in the primary end point (defined as the combination of death from coronary heart disease, nonfatal non-procedural MI, resuscitation after cardiac arrest, or fatal or nonfatal stroke) in patients treated with atorvastatin 80 mg daily compared to patients treated with atorvastatin 10 mg daily. Patients treated with high dose atorvastatin had a decreased incidence of the following components of this primary endpoint: nonfatal MI (HR 0.78, 95% CI 0.66 to 0.93), and fatal or nonfatal stroke (HR 0.75, 95% CI 0.59 to 0.96). Higher intensity treatment was also associated with a lower incidence of the following secondary outcomes: major coronary event (HR 0.80, 95% CI 0.69 to 0.92), cerebrovascular event (HR 0.77, 95% CI 0.64 to 0.93), hospitalisation for congestive heart failure (HR 0.75, 95% CI 0.59 to 0.93), any cardiovascular event (HR 0.81, 95% CI 0.75 to 0.87) and any coronary event (HR 0.79, 95% CI 0.73 to 0.86). There was no difference in all cause mortality between higher and lower intensity atorvastatin treatment (LaRosa, J. C., Grundy, S. M., Waters, D. D. et al 2005).
A fourth trial compared early intensive statin therapy with delayed lower intensity statin therapy (A to Z) (de Lemos, J. A., Blazing, M. A., Wiviott, S. D. et al 2004). This trial consisted of 2 overlapping phases. The first phase was an open labelled trial comparing enoxaprin with unfractionated heparin in patients with non ST elevation acute coronary syndrome who were treated with tirofiban and aspirin. The second phase recruited patients initially from the first phase who had stabilised (for at least 12 consecutive hours within 5 days after symptom onset). In addition, recruits had at least one of the following characteristics: age older than 70 years, diabetes mellitus, prior history of coronary artery disease, peripheral arterial disease or stroke. Subsequently, the protocol was amended to allow patients with non ST elevation acute coronary syndrome who were not enrolled in the first phase, and also patients with ST elevation MI to enter into the second phase directly (overall non ST-segment elevation acute coronary syndrome: 60%, ST elevation MI: 40%).

At baseline almost all the participants were taking aspirin and beta blockers, three quarters were taking ACEIs and almost half were revascularised for treatment of the index event. Patients were randomised to either simvastatin 40 mg once daily for 1 month followed by 80 mg once daily thereafter (early intensive therapy) or placebo for 4 months followed by simvastatin 20 mg once daily thereafter (delayed conservative therapy) (de Lemos, J. A., Blazing, M. A., Wiviott, S. D. et al 2004).

Early high intensity statin therapy decreased LDL cholesterol levels by 39% compared with baseline during the first month of therapy with simvastatin 40 mg and then by a further 6% following an increase in simvastatin dosage to 80 mg. For the delayed conservative statin treatment group, LDL cholesterol levels increased by 11% during the 4 month placebo period, then decreased from baseline by 31% after 4 months of therapy with simvastatin 20 mg (de Lemos, J. A., Blazing, M. A., Wiviott, S. D. et al 2004).

For the primary endpoint of the combination of cardiovascular death, nonfatal MI, readmission for acute coronary syndrome or stroke, early higher intensity statin therapy did not confer benefit compared with delayed lower intensity therapy. There was also no benefit found in any of the individual components of the primary endpoint. Likewise no benefit was observed in the secondary endpoints of all cause mortality and coronary revascularisation due to documented ischaemia. There was a
reduction in the incidence of new onset congestive heart failure in the early intensive
statin treatment group compared with the delayed conservative treatment group (HR
0.72, 95% CI 0.53 to 0.98) but not a reduction in cardiovascular related death (HR
0.75, 95% CI 0.51 to 1.00) (de Lemos, J. A., Blazing, M. A., Wiviott, S. D. et al
2004).

A meta-analysis of these four studies has been conducted by Cannon et al (Cannon,
C. P. et al 2006) using a fixed-effects model. Higher intensity statin therapy did not
confer any significant benefit over lower intensity statin therapy for the outcomes of
all cause mortality (OR 0.94, 95 % CI 0.85 to 1.04), cardiovascular mortality (OR
0.88, 95 % CI 0.78 to 1.00) or non-cardiovascular mortality (OR 1.03, 95 % CI 0.88
to 1.20). Higher intensity statin therapy was associated with a reduction in the
combination of coronary death or MI (OR 0.84, 95 % CI 0.77 to 0.91), stroke (OR
0.82, 95 % CI 0.71 to 0.96) and coronary death or any cardiovascular event (OR
0.84, 95 % CI 0.80 to 0.89).

In addition to the four trials comparing higher intensity therapy with lower intensity
therapy, two randomised controlled trials were identified that compared higher
intensity statin therapy with placebo. The first trial recruited patients with acute
coronary syndrome (Schwartz, G. G. et al 2001) and the second recruited patients
with a history of stroke or transient ischaemic attack (Amarenco, P. et al 2006).

The trial in patients with acute coronary syndrome (Schwartz, G. G., Olsson, A. G.,
Ezekowitz, M. D. et al 2001) randomised a total of 3,086 patients with unstable
angina or non-Q-wave acute MI to receive either atorvastatin 80 mg daily or placebo.
Patients were hospitalised within 24 hours of the index event and randomised after a
mean of 63 hours of hospitalisation. During or after hospitalisation for the index
event, most were treated with aspirin, three quarters with beta blockers and half with
ACE inhibitors or ARBs.

The study period was for 16 weeks and during this period the primary end point
(combination of death, nonfatal acute MI, cardiac arrest with resuscitation, or
recurrent symptomatic myocardial ischemia with objective evidence requiring
emergency rehospitalisation) was not significantly reduced in patients randomised to
atorvastatin compared with those who received placebo (RR 0.84, 95% CI 0.70 to
1. Atorvastatin therapy was not associated with a reduction in the following
2. individual components of the primary outcome: death, non-fatal MI or cardiac arrest
3. with resuscitation but was associated with a lower risk of recurrent myocardial
4. ischaemia requiring rehospitalisation compared with placebo (RR 0.74, 95% CI 0.57
to 0.95). However, it should be noted that the study was only powered to detect
6. differences between groups in the primary outcome. At the end of the study,
7. compared to baseline, LDL cholesterol had increased by an adjusted mean of 12%
8. in the placebo group and had decreased by an adjusted mean of 40% in the

Incidences of the following secondary outcomes were not different in the atorvastatin
10. group compared with placebo: coronary revascularisation procedures, worsening
11. congestive heart failure or worsening angina. Non-fatal stroke was reduced in the
12. atorvastatin group compared with placebo (RR 0.41, 95% CI 0.20 to 0.87) as was
13. the composite outcome of fatal and non-fatal stroke (RR 0.50, 95% CI 0.26 to 0.99)

The second randomised controlled trial (Amarenco, P., Bogousslavsky, J., Callahan,
16. A., III et al 2006) recruited patients without known CHD and with previously
18. documented stroke (69%) (66.5% ischaemic and 2.5% haemorrhagic) or transient
19. ischaemic attack (31%), 1 to 6 months prior to randomisation. A total of 4,731
20. participants were randomised to receive either 80 mg atorvastatin or placebo and
21. were followed up for a mean duration of 4.9 years. Most patients were taking aspirin
22. or other antiplatelets (not heparin) although only 29% were taking ACE inhibitors and
23. 18% beta blockers. For the primary endpoints, high dose atorvastatin decreased the
24. risk of fatal stroke (HR 0.57, 95% CI 0.35 to 0.95) and the composite of fatal and
25. non-fatal stroke (HR 0.84, 95% CI 0.71 to 0.99). No benefit was found for the
26. outcome of non-fatal stroke. Post hoc analysis indicated significant differences in
27. hazard ratios based on the type of stroke occurring during the trial; the cause
28. specific adjusted hazard ratios compared to placebo showed a beneficial effect in
29. those experiencing ischaemic stroke during the trial (HR 0.78, 95% CI 0.66 to 0.94),
30. but a harmful effect on those experiencing hemorrhagic stroke (HR 1.66, 95% CI
31. 1.08 to 2.55). Atorvastatin conferred benefit compared with placebo for the following
32. secondary outcomes: Major coronary event (HR 0.65, 95% CI 0.49 to 0.87), major
cardiovascular event (HR 0.80, 95 % CI 0.69 to 0.92), any cardiovascular event (HR 0.74, 95 % CI 0.66 to 0.83), acute coronary event (HR 0.65, 95 % CI 0.50 to 0.84), any coronary event (HR 0.58, 95 % CI 0.46 to 0.73), non-fatal MI (HR 0.51, 95 % CI 0.35 to 0.74), revascularisation (HR 0.55, 95 % CI 0.43 to 0.72), transient ischaemic attack (HR 0.74, 95 % CI 0.60 to 0.91), the composite of stroke or transient ischaemic attack (HR 0.77, 95 % CI 0.67 to 0.88). No benefit was seen for the outcomes of cardiovascular mortality or all cause mortality (Amarenco, P., Bogousslavsky, J., Callahan, A., III et al 2006) but the trial was not statistically powered for this endpoint.

9.3.4 Cost effectiveness of statins

The NICE Technology Appraisal (NICE technology appraisal guidance 94, Statins for the prevention of cardiovascular events’ 2006) states that:

- When the decision has been made to prescribe a statin, it is recommended that therapy should usually be initiated with a drug of low acquisition cost (taking into account required daily dose and product price per dose).

9.3.5 Cost effectiveness of higher intensity statin therapy compared with lower intensity statin therapy

When initial searches were done no studies were found which compared cost effectiveness of higher intensity statins with lower intensity statins in patients with coronary artery disease (CAD). The GDG requested an economic analysis to help inform the decisions of the guideline group. The full economic analysis can be found in Appendix C.

A Markov model was developed to evaluate the incremental costs and effects of lifetime treatment from a UK NHS perspective and the base case results were presented for 65-year-old men and women with coronary artery disease. Effectiveness data was drawn from 4 studies which were meta-analysed; A to Z (de Lemos, J. A., Blazing, M. A., Wiviott, S. D. et al 2004), TNT (LaRosa, J. C., Grundy, S. M., Waters, D. D. et al 2005), IDEAL (Pedersen, T. R., Faergeman, O., Kastelein, J. J. et al 2005), and PROVE-IT (Cannon, C. P., Braunwald, E., McCabe, C. H. et al
In a sensitivity analysis we separated the results of trials after acute coronary syndrome (ACS) from those including more stable coronary artery disease. The results suggested that treatment with higher intensity statin is cost effective in the prevention of CVD when compared to lower intensity statin. The ICER of higher intensity statin compared with lower intensity statin is about £14,000 per QALY which is below the level usually considered to be affordable in the NHS (about £20,000 to £30,000 per QALY). The result is sensitive to age, treatment effect on mortality, health state utility assumptions on MI, and loss in quality of life due to treatment side effects. When data from the ACS population alone were used, the results become more favorable with ICERs falling to about £7,600/QALY. This may be explained by the difference in mortality seen in ACS patients, relative risk 0.75 (95% CI 0.63-0.93). When results of patients with stable CAD are considered alone, the use of higher intensity statins compared with lower intensity statins is not cost effective when a £20,000/QALY threshold is used. Higher intensity statins are dominated by lower intensity statins. That is to say in people with more stable CAD, higher intensity statins are more costly and result in less quality adjusted life years than the use of lower intensity statins.

Updated searches retrieved one study which compared higher intensity statins with lower intensity statins in patients with acute coronary syndrome (ACS) and stable coronary artery disease (CAD) Chan (Chan, P. S. et al 2007). It was a cost utility analysis, and they used a Markov model for a hypothetical population of 60 year olds from a US perspective. Effectiveness data was drawn from A to Z (de Lemos, J. A., Blazing, M. A., Wiviott, S. D. et al 2004), PROVE-IT (Cannon, C. P., Braunwald, E., McCabe, C. H. et al 2004) for the ACS population and from TNT (LaRosa, J. C., Grundy, S. M., Waters, D. D. et al 2005), IDEAL (5231 for the stable CAD population. The use of higher intensity statins was found to be cost effective in ACS with ICERs of less than $30,000/QALY and stable in sensitivity analysis. The result for stable CAD was cost effective for the base model $33400/QALY but very sensitive to assumptions about statin efficacy and the resulting reduction in cardiovascular events and also on the difference in statin costs between higher and lower intensity statins.
In conclusion our base model showed that higher intensity statins are cost effective in the treatment of people with coronary artery disease. This finding is however dependent on treatment effect and the absolute reduction in mortality. Sensitivity analysis showed that results are more favourable for those patients after recent acute coronary syndrome and also demonstrated that in patients with stable CAD higher intensity statins may not be cost effective.

9.3.6 Adverse events associated with lower intensity statin therapy

Adverse events associated with lower intensity statin therapy are discussed in the primary prevention drug therapy chapter (Section 6.3.2.3).

9.3.7 Adverse events associated with higher intensity statin therapy

Four randomised controlled trials were identified that compared higher intensity statin therapy with lower intensity statin therapy, the details and results of which have been described in section 1.3.3 {Cannon, 2004 5232 /id} (Pedersen, T. R., Faergeman, O., Kastelein, J. J. et al 2005) (LaRosa, J. C., Grundy, S. M., Waters, D. D. et al 2005) (de Lemos, J. A., Blazing, M. A., Wiviott, S. D. et al 2004).

The first trial (Cannon, C. P., Braunwald, E., McCabe, C. H. et al 2004) found elevations in alanine aminotransferase levels to be greater in patients who received atorvastatin 80 mg compared with those receiving pravastatin 40 mg.

Discontinuation of study medication due to myalgia, muscle aches or elevations in creatine kinase levels were similar in the two treatment groups. No cases of rhabdomyolysis were reported in either group (Cannon, C. P., Braunwald, E., McCabe, C. H. et al 2004).

The second trial (Pedersen, T. R., Faergeman, O., Kastelein, J. J. et al 2005) found that patients who received atorvastatin 80 mg had higher rates of discontinuation due to non-serious adverse events than those allocated to simvastatin 20 mg. There were no differences in the frequency of serious adverse events between the two treatment groups. Serious myopathy and rhabdomyolysis were rare in both groups (Pedersen, T. R., Faergeman, O., Kastelein, J. J. et al 2005).
The third trial (LaRosa, J. C., Grundy, S. M., Waters, D. D. et al 2005) found therapy with atorvastatin 80 mg to be associated with an increase in adverse events, with a higher rate of treatment discontinuation compared with the atorvastatin 10mg group. Treatment related myalgia was similar in the two groups and there were no persistent elevations in creatine kinase. Five cases of rhabdomyolysis were reported (2 in the high dose group, 3 in the low dose group). More patients in the high dose group had persistent elevation in alanine aminotransferase, aspartate aminotransferase or both, compared with the low dose group (LaRosa, J. C., Grundy, S. M., Waters, D. D. et al 2005).

The fourth trial (de Lemos, J. A., Blazing, M. A., Wiviott, S. D. et al 2004) compared early intensive therapy (simvastatin 40 mg once daily for 1 month followed by 80 mg once daily thereafter) with delayed conservative therapy (placebo for 4 months followed by simvastatin 20 mg once daily thereafter). Incidences of elevated alanine aminotransferase or aspartate transaminase levels (greater than 3 X ULN) were found to be similar in the two treatment groups. Discontinuation of study medication due to muscle-related adverse events was also comparable between the two groups. A total of 10 patients developed myopathy (creatine kinase > 10 X ULN on 2 consecutive measurements). Of the nine patients treated with simvastatin 80 mg, three patients had creatine kinase levels > 10 000 units/l and met the criteria for rhabdomyolysis. Of these 3 patients, 1 had contrast media renal failure and 1 patient was receiving concomitant verapamil (inhibitor of cytochrome P450 3A4 (CYP3A4)). In addition, 1 patient receiving 80 mg simvastatin had a creatine kinase level 10 X ULN without muscle symptoms, which was associated with alcohol abuse (de Lemos, J. A., Blazing, M. A., Wiviott, S. D. et al 2004).

Two randomised controlled trials were identified that compared higher intensity statin therapy with placebo (Amarenco, P., Bogousslavsky, J., Callahan, A., Ill et al 2006) (Schwartz, G. G., Olsson, A. G., Ezekowitz, M. D. et al 2001), the details and results of which have also been described in section 9.3.3.

The first trial (Schwartz, G. G., Olsson, A. G., Ezekowitz, M. D. et al 2001) found that more patients in the atorvastatin 80mg group developed liver transaminase levels > 3 X ULN compared with those allocated placebo. There were no cases of myositis.
The second trial (Amarenco, P., Bogousslavsky, J., Callahan, A., III et al 2006) compared treatment with atorvastatin 80 mg to placebo and found no significant difference in the incidence of serious adverse events between groups, although persistent elevation of alanine or aspartate aminotransferase (> 3 ULN on two consecutive occasions) was more frequent in the atorvastatin group (2.2 %) versus placebo (0.5 %), \( P < 0.001 \).

A retrospective analysis of pooled data from 49 clinical trials of atorvastatin was identified which compared the relative safety of lower intensity atorvastatin 10 mg with higher intensity atorvastatin 80 mg (Newman, C. et al 2006). Data were pooled from 49 clinical trials \((n = 14,236\) participants) in which patients were randomised to receive active treatment for a period ranging from 2 weeks to 52 months \(\text{atorvastatin 10 mg: } n = 7,258, \text{ atorvastatin 80 mg: } n = 4,798\) and placebo: \(n = 2,180\). The incidence rate \((\text{per 1000 patient-years of exposure})\) of various safety parameters and adverse events was calculated for each of the three groups. The overall safety profile was comparable between atorvastatin 80 mg, 10 mg and placebo in terms of incidence rate of patients experiencing \(\geq 1\) adverse event, withdrawals due to adverse events and serious, nonfatal adverse events. Musculoskeletal safety parameters were also similar across groups and there were no incidences of myopathy or rhabdomyolysis reported. In this analysis, a greater incidence of persistent alanine aminotransferase \(> 3 \times \text{ULN}\) was observed in the atorvastatin 80 mg group compared with the other two groups. Serious hepatic adverse events were rare although five patients in the atorvastatin 80 mg group developed hepatitis, which resolved after discontinuation of atorvastatin. The adverse events of haematuria and albuminuria were also examined but the incidence in each atorvastatin group was low compared to placebo. Incidence of death was low in all groups and none were considered to be related to treatment.

A further study has examined the safety of rosuvastatin used in clinical practice (sheikh-Ali, A. A. et al 2005). The study reviewed adverse event reports (AERs) to the Food and Drug Administration USA (FDA) to determine the frequency of rosuvastatin-associated events relative to other commonly used statins, namely; atorvastatin, simvastatin, pravastatin and cerivastatin (for cerivastatin during the time...
Two comparative primary analyses were performed. For the first analysis, AERs were determined for the first year during which rosuvastatin was available in the USA (October 2003 to September 2004) and these AERs were compared with the concomitant time period for the other statins (defined as ‘concurrent time period analysis’). The mean doses of statins during this time period was as follows; rosuvastatin 16.7±1.2 mg, simvastatin 53±2.8 mg, pravastatin 18.8±2.0 mg and atorvastatin 21.8±1.4 mg. The second analysis was performed to address the potential of preferential reporting of adverse events with newly marketed drugs. Thus rates of rosuvastatin-associated AERs were compared with those during the first year of marketing for atorvastatin (1997), simvastatin (1992), pravastatin (1992) and cerivastatin (1998). This was defined as ‘first year of marketing analysis’.

For the concurrent time period analysis, the rate of rosuvastatin AERs (a composite of rhabdomyolysis, proteinuria / nephropathy, or renal failure) was higher than AERs for simvastatin ($P < 0.001$), pravastatin ($P < 0.001$) and atorvastatin ($P < 0.001$). For the first year of marketing analysis the rate of rosuvastatin-associated composite AERs was not significantly different than simvastatin AERs, but was significantly higher compared with pravastatin ($P < 0.001$) and atorvastatin ($P < 0.001$).

Compared with AERs for cerivastatin during its first post marketing year, rosuvastatin composite AERs were less frequent ($P < 0.001$). Sixty two percent of rosuvastatin-associated AERs occurred at doses of $\leq 10$ mg / day, and occurred earlier after the initiation of therapy (within the first 12 weeks) compared to other statins. There was no gender predominance. While fatalities were rare, most composite AERs listed hospitalisation as an outcome (sheikh-Ali, A. A., Ambrose, M. S., Kuvin, J. T. et al 2005).

The increased rate of rosuvastatin-associated AERs relative to the other statins was also observed in secondary analysis.

For the concurrent time period analysis, the rate of rosuvastatin-associated AERs for any adverse event was higher than that observed for simvastatin, pravastatin and atorvastatin ($P < 0.001$ all statins versus rosuvastatin). Likewise for serious AERs.
(life threatening or requiring hospitalisation), liver AERs, muscle AERs without rhabdomyolysis and also renal failure AERs, rosuvastatin had higher rates of adverse events ($P < 0.001$ all statins versus rosuvastatin). Furthermore, rhabdomyolysis AERs, although rare, were also higher for rosuvastatin (simvastatin; $P < 0.01$, pravastatin and atorvastatin; $P < 0.001$) (sheikh-Ali, A. A., Ambrose, M. S., Kuvin, J. T. et al 2005).

For the first year of marketing analysis the rate of rosuvastatin-associated AERs was similarly higher for the following AERs compared with other statins; all AERs (simvastatin, pravastatin atorvastatin, cerivastatin $P < 0.001$ all statins versus rosuvastatin), muscle AERs without rhabdomyolysis (simvastatin, pravastatin atorvastatin, cerivastatin $P < 0.001$ all statins versus rosuvastatin). Liver AERs were higher for rosuvastatin compared with simvastatin, pravastatin and atorvastatin, but were not significantly different with the rate observed with cerivastatin. Serious AERs were higher for rosuvastatin compared with pravastatin and atorvastatin ($P < 0.001$ for both); however, the rosuvastatin rate was lower than that observed for simvastatin ($P < 0.001$) and cerivastatin ($P < 0.01$). Rosuvastatin was also significantly more likely than simvastatin, pravastatin and atorvastatin to be associated with reports of rhabdomyolysis ($P < 0.001$ all statins versus rosuvastatin), but compared with the first year of cerivastatin, the rate of rosuvastatin rhabdomyolysis events was significantly less ($P < 0.001$). Finally, the rate of rosuvastatin-associated renal failure AERs was higher compared with pravastatin and atorvastatin ($P < 0.001$ for both), but similar to that observed with simvastatin and cerivastatin (sheikh-Ali, A. A., Ambrose, M. S., Kuvin, J. T. et al 2005).

There are a number of intrinsic limitations of post marketing adverse event analysis. The analysis are based on reporting rates, not on actual adverse event rates. In clinical practice, adverse events are under reported, and serious adverse events are more likely to be reported than less serious events. The retrospective nature of the analysis does not allow confirmation of causality, or control of potential confounders. For example, providers tend to report preferentially adverse events with newly marketed drugs. In addition, certain adverse events may not be recognised as related to a particular class of drug. Post marketing analysis can also be influenced by publicity, favourably or unfavourably. Another time dependent post marketing
variable could be related to the availability of drug dosage. In this context, the relatively low rate of atorvastatin-associated AERs during its first year of marketing may be partially attributable to the fact that only the 10 mg dose was available in the first year (sheikh-Ali, A. A., Ambrose, M. S., Kuvin, J. T. et al 2005).

Not with standing these limitations, the review found that rosuvastatin had a higher rate of AERs compared with other commonly prescribed statins based upon adverse event reports to the FDA. The authors of the review stated that the reported occurrence of these AERs early after initiation of therapy (within 12 weeks on average) suggests that vigilant monitoring for adverse events may ameliorate the risk of toxicity when rosuvastatin is used. They also stated that it would seem prudent for healthcare providers to consider other statins as first line therapy, to initiate rosuvastatin therapy in appropriate patients at lower doses as well as careful monitoring for adverse events (sheikh-Ali, A. A., Ambrose, M. S., Kuvin, J. T. et al 2005).

9.3.8 Evidence to recommendations – statins

The NICE technology appraisal on statins (NICE technology appraisal guidance 94, Statins for the prevention of cardiovascular events' 2006) considered twenty-eight randomised controlled trials of statins in adults with or at risk of CVD.

No studies that reported cardiovascular events as outcomes were identified for rosuvastatin. Fourteen placebo-controlled studies in which all participants had CHD at study entry were identified for inclusion in a meta-analysis. There were significant reductions in all cause mortality (RR 0.79, 95% CI 0.70 to 0.90), CVD mortality (RR 0.75, 95% CI 0.68 to 0.83), CHD mortality (RR 0.72, 95% CI 0.64 to 0.80), fatal MI (RR 0.57, 95% CI 0.45 to 0.72), nonfatal MI (RR 0.69, 95% CI 0.59 to 0.95), new or worsening intermittent claudication (RR 0.64, 95% CI 0.46 to 0.91). There was no significant reduction in stroke mortality (RR 1.07, 95% CI 0.67 to 1.71) or TIA (RR 0.66 95% CI 0.37 to 1.17). The relative effectiveness of statins did not differ by sex, in people with and without diabetes, or in people over 65 years compared with younger people. For secondary CHD prevention the incremental cost per QALY ranged from £10,000 to £16,000 for all age groups with little difference for men and women.
The NICE technology appraisal (NICE technology appraisal guidance 94, ‘Statins for
the prevention of cardiovascular events’ 2006) recommended statin therapy for all
adults with clinical evidence of CVD and that when the decision has been made to
prescribe a statin, it is recommended that therapy should usually be initiated with a
drug with a low acquisition cost (taking into account required daily dose and product
price per dose). The GDG considered that for initiation of treatment, simvastatin 40
mg was the most effective drug with a low acquisition cost in secondary prevention.

9.3.8.1 The use of higher intensity statins and cholesterol targets

Within the GDG there were differing views on the use of cholesterol “targets” i.e.
levels of total and LDL cholesterol that all patients on lipid lowering therapy should
either aim to be below or should achieve. International and national guidelines on
lipid lowering for CVD prevention have all defined goals or targets of therapy. These
target levels have become progressively lower over time and differ between
guidelines. The Joint British Societies first recommended a total cholesterol target of
less than 5.0 mmol/l and an LDL cholesterol target of less than 3.0 mmol/l, or a
25% total cholesterol reduction or a 30% LDL cholesterol reduction, whichever is
greater, in 1998 (Scottish Intercollegiate Guidelines Network 1999). The National
Service Framework for CHD in 2000 recommended levels less than total cholesterol
5 mmol/l or LDL cholesterol 3 mmol/l (or a 25% TC reduction or 30% LDL
cholesterol reduction whichever is greater) and these remain the current national
advice (DoH March 2000 website). In 2003 the Joint European Societies Task Force
on CVD Prevention recommended a total cholesterol less than 4.5 mmol/l and LDL
cholesterol levels below 2.5 mmol/l. Since 2004 in the USA high risk CVD patients
are advised to achieve LDL cholesterol levels below 1.81 mmol/l

The most recent Joint British Societies 2005 guideline recommends target levels
below total cholesterol 4 mmol/l and LDL cholesterol 2 mmol/l (or a 25% reduction in
total cholesterol and a 30% reduction in cholesterol if that yields a lower value)
(2005). The Scottish Sign Guideline 2007 considers total cholesterol targets of 4
mmol/l or 4.5 mmol/l would have major resource implications for NHS Scotland
(Scottish Intercollegiate Guidelines Network. 2007), but this was not based on a
formal cost-effectiveness analysis. SIGN recommends that pending further studies
on mortality, safety and cost-effectiveness, a total cholesterol target of less than 5
mmol/l in individuals with CVD should be a minimum standard of care (Scottish
Intercollegiate Guidelines Network. 2007).

GDG discussion on use of targets

Those supporting targets point out that the Cholesterol Trialists Collaboration
(Baigent, C., Keech, A., Kearney, P. M. et al 2005) reported an approximately linear
relationship between the absolute reductions in LDL cholesterol achieved in these
trials and the proportional reductions in the incidence of coronary and other events.
The proportional reduction in the event rate per mmol/l reduction in LDL cholesterol
was largely independent of the presenting cholesterol level. So lowering the LDL
cholesterol level from 4 mmol/l to 3 mmol/l reduced the risk of vascular events by
about 23% and lowering LDL cholesterol from 3 mmol/l to 2 mmol/l also reduced
residual risk by about 23%. There is a linear relationship between the log of the risk
and cholesterol reduction but it is important to appreciate that although the relative
risk reduction remains constant, at lower cholesterol levels there is a smaller
absolute reduction in cardiovascular events and it is absolute risk reduction that
determines cost-effectiveness.

This log linear relationship is a robust description of the effect of cholesterol lowering
with statins, at least down to a LDL cholesterol of 2 mmol/l. A meta-analysis of higher
intensity statins (Cannon, C. P., Steinberg, B. A., Murphy, S. A. et al 2006)
confirmed that the observed 0.67 mmol/l reduction in LDL cholesterol would be
expected to lead to a 14% reduction in cardiovascular events on the basis of the log
linear hypothesis and the observed reduction of 16% was consistent with this.
Proponents of targets consider that the log linear hypothesis supports the use of
targets because they consider it confirms that for LDL cholesterol “lower is better”.

The use of targets as low as 2 mmol/l has however been challenged and a number
of objections have been made to targets as a driver for drug treatment to lower

A particular concern is that in practice, targets are interpreted to mean that all
patients on treatment should attain the recommended level irrespective of their
starting cholesterol. This takes no account of the distribution of cholesterol in the
population which ranges from high to low, nor of differing responses to treatment and
differing adherence to treatment. Cholesterol targets of 2 mmol/l will not be achieved
by many if not most patients using statins with trial evidence of reduction in
cardiovascular events.

This is illustrated below in Figure 1 showing average baseline and achieved LDL
cholesterol levels in different statin trials. Drug trials report average values, half the
people have levels above this average value. LDL cholesterol was reduced below
an average value of 2 mmol/l in only three of the twenty trials shown; PROVE-IT 1.6
(de Lemos, J. A., Blazing, M. A., Wiviott, S. D. et al 2004), MIRACL 1.9 mmol/l
Schwartz, G. G., Olsson, A. G., Ezekowitz, M. D. et al 2001). These were all recent
trials of statins at maximal licensed dosage. Two other higher dose trials achieved
levels of 2.0 mmol/l (TNT) (LaRosa, J. C., Grundy, S. M., Waters, D. D. et al 2005)
and 2.1 mmol/l (IDEAL) (Pedersen, T. R., Faergeman, O., Kastelein, J. J. et al
2005). CARDS (Colhoun, H. M., Betteridge, D. J., Durrington, P. N. et al 2004) at a
dose of atorvastatin 10 mg achieved a level of 2.0 mmol/l. These trials had strict
recruitment criteria and patients with higher levels of LDL cholesterol tended to be
excluded. These trials are therefore not representative of the general population with
CVD who would be less likely to achieve such low levels as those in included in the
trials. It is misleading for both professionals and patients, to set a target that is
interpreted as ‘should be achieved’, knowing that many patients will not achieve this.
The second objection to targets as a basis for treating people with higher intensity statins or drug combinations are concerns that at low levels of cholesterol there are small and decreasing absolute returns from treatment but a greater propensity for adverse effects from drugs at maximal dose or from combinations of drugs (Magi, L. et al 2006).

Two-thirds of the gain from a statin is realised by the initial dose. Lower cholesterol for individual patients may be achieved by doubling doses of statins or using higher intensity statins. Each doubling in dose of statin will only lower cholesterol by a further 6%, while the risk of adverse events may increase. For each doubling of dose there is a smaller and smaller absolute reduction in CVD events. This has led to
doubts about the cost-effectiveness of the additional benefit of higher intensity statins over lower intensity statins.

Finally, there is no trial evidence that drug combinations such as statin plus fibrate, or statin plus ezetimibe will produce additional cost-effective absolute reductions in cardiovascular events.

The GDG concluded by majority that the use of higher intensity statins or drug combinations should be driven by trial evidence of absolute benefit in clinical outcomes, not by targets and relative risk. There was concern that the adoption of targets may encourage the indiscriminate use of either high dose statins or combination lipid therapy, the latter not having been shown to reduce cardiovascular events.

9.3.8.2 When to use higher intensity statins

The question arises; when should clinicians use higher intensity statins rather than lower intensity statins?

Both absolute risk and absolute reduction in cholesterol levels determine the absolute benefits from treatment. Should people start treatment with a lower intensity statin and titrate up to the maximal tolerated dose on the basis of their cholesterol? Or should people simply be started on the maximal dose without delay?

The log linear hypothesis indicates that the greatest absolute benefit from statins will be achieved in people with the highest level of cholesterol because they have the furthest to fall on treatment. As the baseline LDL cholesterol level falls the absolute benefits of treatment are fewer. The Cholesterol Trialists report (Baigent, C., Keech, A., Kearney, P. M. et al 2005) concluded “treatment goals for statin treatment should aim chiefly to achieve substantial absolute reductions in LDL cholesterol (rather than to achieve particular target levels of LDL cholesterol)”. It is the absolute benefits that drive policy and the GDG preferred a strategy that favours higher intensity statin treatment in people with the highest cholesterol as they are likely to experience greatest absolute benefit. The GDG considered that most advantage would be gained by more intensive treatment in people with higher cholesterol levels. The GDG consider that titration to a higher intensity statin should be recommended
where a total cholesterol level of 4 mmol/l or an LDL cholesterol level of 2 mmol/l is not achieved using simvastatin 40 mg as the initial treatment in secondary prevention. A target level is not recommended. An audit level of total cholesterol 5 mmol/l may help to assess progress in populations and groups.

### Table 3: Absolute LDL cholesterol reduction* and percentage reductions# in serum

LDL cholesterol concentration according to statin and daily dose (summary estimates from 164 randomised controlled trials)

<table>
<thead>
<tr>
<th>Statin</th>
<th>Daily dose (mg)</th>
<th>Absolute LDL cholesterol reduction (mmol/l) (95% confidence intervals)</th>
<th>Percentage reduction LDL cholesterol in serum</th>
</tr>
</thead>
<tbody>
<tr>
<td>atorvastatin</td>
<td>10</td>
<td>1.79 (1.62 to 1.97)</td>
<td>37%</td>
</tr>
<tr>
<td>atorvastatin</td>
<td>20</td>
<td>2.07 (1.90 to 2.25)</td>
<td>43%</td>
</tr>
<tr>
<td>atorvastatin</td>
<td>40</td>
<td>2.36 (2.12 to 2.59)</td>
<td>49%</td>
</tr>
<tr>
<td>atorvastatin</td>
<td>80</td>
<td>2.64 (2.31 to 2.96)</td>
<td>55%</td>
</tr>
<tr>
<td>pravastatin</td>
<td>40</td>
<td>1.38 (1.31 to 1.46)</td>
<td>29%</td>
</tr>
<tr>
<td>rosuvastatin</td>
<td>5</td>
<td>1.84 (1.74 to 1.94)</td>
<td>38%</td>
</tr>
<tr>
<td>rosuvastatin</td>
<td>10</td>
<td>2.08 (1.98 to 2.18)</td>
<td>43%</td>
</tr>
<tr>
<td>rosuvastatin</td>
<td>20</td>
<td>2.32 (2.20 to 2.44)</td>
<td>48%</td>
</tr>
<tr>
<td>simvastatin</td>
<td>40</td>
<td>1.78 (1.66 to 1.90)</td>
<td>37%</td>
</tr>
<tr>
<td>simvastatin</td>
<td>80</td>
<td>2.01 (1.83 to 2.19)</td>
<td>42%</td>
</tr>
</tbody>
</table>

* Absolute reductions are standardised to usual LDL cholesterol concentration of 4.8 mmol/l before treatment (mean concentration in trials). #Percentage reductions are independent of pre-treatment LDL cholesterol concentration; 95% confidence intervals on percentage reductions can be derived by dividing those on absolute reductions by 4.8.
**Table 2:** Absolute cholesterol reduction* and percentage reductions# in serum total cholesterol concentration according to statin and daily dose (summary estimates from 164 randomised controlled trials)

<table>
<thead>
<tr>
<th>Statin</th>
<th>Daily dose (mg)</th>
<th>Absolute total cholesterol reduction (mmol/l) (95% confidence intervals)</th>
<th>Percentage reduction total cholesterol in serum</th>
</tr>
</thead>
<tbody>
<tr>
<td>atorvastatin</td>
<td>10</td>
<td>2.15 (1.94 to 2.33)</td>
<td>32%</td>
</tr>
<tr>
<td>atorvastatin</td>
<td>20</td>
<td>2.45 (2.28 to 2.70)</td>
<td>36%</td>
</tr>
<tr>
<td>atorvastatin</td>
<td>40</td>
<td>2.83 (2.54 to 3.11)</td>
<td>42%</td>
</tr>
<tr>
<td>atorvastatin</td>
<td>80</td>
<td>3.17 (2.77 to 3.55)</td>
<td>47%</td>
</tr>
<tr>
<td>pravastatin</td>
<td>40</td>
<td>1.99 (1.88 to 2.10)</td>
<td>29%</td>
</tr>
<tr>
<td>rosuvastatin</td>
<td>5</td>
<td>2.21 (2.09 to 2.33)</td>
<td>33%</td>
</tr>
<tr>
<td>rosuvastatin</td>
<td>10</td>
<td>2.50 (2.38 to 2.62)</td>
<td>37%</td>
</tr>
<tr>
<td>rosuvastatin</td>
<td>20</td>
<td>2.74 (2.64 to 2.93)</td>
<td>40%</td>
</tr>
<tr>
<td>simvastatin</td>
<td>40</td>
<td>2.14 (1.99 to 2.28)</td>
<td>31%</td>
</tr>
<tr>
<td>simvastatin</td>
<td>80</td>
<td>2.41 (2.20 to 2.63)</td>
<td>35%</td>
</tr>
</tbody>
</table>

*Absolute reductions are standardised to usual total cholesterol concentration of 6.8 mmol/l before treatment (mean concentration in trials). #Percentage reductions are independent of pre-treatment total cholesterol concentration; 95% confidence intervals on percentage reductions can be derived by dividing those on absolute reductions by 6.8.
9.3.8.3  *Is titration to high intensity statins appropriate for both acute and stable CHD and all secondary CVD?*

The GDG considered whether the results of the trials of higher intensity statins were generalisable to all CVD, only to acute CHD or to both stable and acute coronary heart disease. The GDG noted that the results of the cost-effectiveness analysis were most robust for acute CHD and that the results of cost-effectiveness studies were (at a given cost) largely predicated on baseline absolute risk (Cost effectiveness analysis 9.3.5). There are no studies of higher versus lower intensity statins for stroke or PAD though there is evidence of benefit for the former against placebo.

Whilst the absolute risks associated with stable CHD are undoubtedly less than those in the acute situation, there is nevertheless considerable heterogeneity of risk amongst people after an acute event and among those who are apparently stable and there are considerable difficulties in deciding which individuals or subgroups are at more or less risk at varying times after a new event. The GDG considered the underlying disease process is the same and that all people with CVD are at sufficient absolute risk of a recurrent event that consideration for treatment with a higher intensity statin is warranted where initial treatment does not reduce total cholesterol to 4 mmol/l or LDL cholesterol to 2 mmol/l or less.

9.3.8.4  *Cost effectiveness of treating to target (titration threshold) compared with fixed doses of statins*

The GDG was interested in answering the question of cost effectiveness of a policy of treating to target (titration strategy) compared to a policy of fixed doses of statins. The systematic literature search identified 408 papers. Eighteen papers were assessed in full and none of them met the inclusion criteria.

The analysis requested by the GDG compared fixed dose of simvastatin 40 mg (GDG agreed no patients will be started on higher intensity statins, hence the fixed dose considered was simvastatin 40 mg) with a titration strategy in which patients are incrementally given simvastatin 40 mg and 80 mg in order to reduce serum cholesterol to 5 mmol/l or less. If patients did not achieve 5 mmol/l or less on simvastatin 80 mg, they are given atorvastatin 80 mg and it was assumed all patients...
will achieve target once they are on atorvastatin 80 mg. The definition of success or
effectiveness was defined as the proportion of patients achieving a total cholesterol
level of less than or equal to 5 mmol/l or percentage reduction in total cholesterol.
The percentage reductions in cholesterol levels were taken from the STELLAR trial
{Jones, 2004 5179 /id} and translated to reduction in final outcomes by use of
The base case results are presented by age and baseline total cholesterol levels.
The results suggest that for younger men and women aged up to 45 years, the
titration strategy has borderline cost effectiveness compared with a fixed lower dose
of statins at a threshold ICER of £20,000/QALY. Up to 45 years titration strategy
compared to fixed lower dose has an estimated ICER of between £18,800-
£20,000/QALY for total cholesterol levels of between 7.5 mmol/l and 5.5 mmol/l
respectively. For age groups above 45 years, the titration strategy is cost effective
compared to a fixed lower dose of statin. Titration strategy compared to a fixed lower
dose has an estimated ICER of between £7,700-£15,200/QALY for men and women
aged between 55 to 75 years. The ICERs are more favourable for the elderly.
In conclusion, the strategy of titration is cost effective when compared to the strategy
of a fixed dose of Simvastatin 40mg for those age groups above 45 years. For age
groups up to 45 years there is borderline cost effectiveness in favour of titration
strategy. Full details of the economic analysis are available in Appendix C.
9.4 Fibrates

9.4.1 Evidence statements for fibrates

9.4.1.1 Two randomised controlled trials in patients after an MI and / or with angina found that clofibrate therapy was not associated with a reduction in fatal MI or sudden death in people with angina compared with placebo. One trial found that clofibrate therapy was not associated with a reduction in cardiovascular morbidity compared with placebo while the other found that clofibrate therapy was associated with a reduction in the rate of first non-fatal infarct in women with a history of angina compared with placebo.

9.4.1.2 One randomised controlled trial in patients after an MI and / or with angina found that bezafibrate therapy was not associated with a reduction in the composite of fatal MI, non-fatal MI and sudden death compared with placebo. In addition, no benefit was seen for cardiovascular morbidity.

9.4.1.3 One randomised controlled trial in men after an MI and / or with angina found that gemfibrozil therapy was associated with a reduction in the composite of fatal MI, sudden death, death due to congestive heart failure and death as a complication of invasive cardiac procedures compared with placebo.

9.4.1.4 Two randomised controlled trials in patients following stroke or TIA found that clofibrate therapy was not associated with a reduction in all cause mortality or cardiovascular morbidity compared with placebo.

9.4.1.5 One randomised controlled trial in patients with peripheral arterial disease showed that bezafibrate therapy was not associated with a reduction in the combination outcome of fatal and nonfatal CHD events and stroke compared with placebo although bezafibrate therapy was associated with a reduction in the incidence of non-fatal coronary heart disease.

9.4.2 Clinical effectiveness of fibrates
The largest randomised controlled trial (n = 9795) investigating the effects of long-term fibrate therapy on CHD event rates was the Fenofibrate Intervention and Event Lowering in Diabetes (FIELD) study (Keech, A. et al 2005). This trial was, however, excluded as it recruited patients with type 2 diabetes mellitus, a population group that is outside the scope of this guidance.

Seven randomised controlled trials were identified that compared fibrate therapy with placebo in patients with a history of CVD. Four of these were in patients after an MI and/or with angina, two were in patients following a stroke or transient ischaemic attack and one was in patients with peripheral arterial disease.

Four randomised controlled trials were identified in patients after an MI and/or with angina (Behar, S. et al 2000) (Rubins, H. B. et al 1999) (Research committee of the Scottish Society of Physicians 1971), (Group of physicians of the Newcastle Upon Tyne region 1971).

The first randomised controlled trial (Research committee of the Scottish Society of Physicians 1971) recruited patients aged 40-69 years with a history of angina, MI or both (27% had angina only). A total of 717 patients were randomised to receive either clofibrate or placebo (olive oil) and were followed up for a mean duration of 4 years. In patients with a history of angina only, treatment with clofibrate did not decrease the rates of sudden death, fatal MI or first non-fatal MI compared to placebo.

The second randomised controlled trial (Group of physicians of the Newcastle Upon Tyne region 1971) recruited patients under 65 years with a history of angina, MI or both (40% had angina only). A total of 497 patients were randomised to receive either clofibrate or placebo (corn oil) and were followed up for 5 years. In patients with a history of angina only, treatment with clofibrate did not decrease the rates of sudden death or fatal MI compared to placebo but was found to decrease the rate of first non-fatal infarct compared to placebo in women with a history of angina ($P < 0.05$) but not men.

Both of these studies used the drug clofibrate which has now been withdrawn from the British National Formulary.
The third randomised controlled trial (Rubins, H. B., Robins, S. J., Collins, D. et al 1999) recruited men with an HDL cholesterol of 1.0 mmol/l or less, LDL cholesterol 3.6 mmol/l or less and triglycerides less than 3.4 mmol/l with documented coronary artery disease defined as a history of MI, angina, having undergone coronary revascularization, or angiographic evidence of coronary stenosis. Of these, 61% had a prior history of MI. Concomitant drug therapy at the start of the trial was as follows; aspirin 82%, beta blockers 43%, nitrates 46%, ACE inhibitors 21%, calcium channel blockers 53%. Patients were randomised to either gemfibrozil or placebo. Patients were followed for a mean 5.1 years. Gemfibrozil therapy was associated with a reduction in the primary endpoint of a combination of nonfatal MI and death from CHD compared with placebo. The incidence of the secondary outcome of a combination of nonfatal MI, death from CHD and confirmed stroke was also reduced in the gemfibrozil treatment group compared with the placebo. In addition, gemfibrozil therapy was associated with a reduction in the following outcomes compared with placebo: nonfatal MI, investigator-designated stroke, transient ischaemic attack, carotid endarterectomy and hospitalisation for congestive heart failure. Treatment with gemfibrozil was not associated with any benefit for the following outcomes: death due to coronary heart disease, death from any cause, confirmed stroke, revascularisation, coronary artery bypass graft, percutaneous transluminal coronary angioplasty, peripheral vascular surgery and hospitalisation for unstable angina.

Patients assigned to gemfibrozil had lower total cholesterol and triglycerides levels and higher HDL cholesterol levels compared to patients in the placebo group. LDL cholesterol levels were the same in both groups. Gemfibrozil treatment was associated with a greater incidence of dyspepsia (Rubins, H. B., Robins, S. J., Collins, D. et al 1999).

The fourth randomised controlled trial (Behar, S., Brunner, D., Kaplinsky, E. et al 2000) recruited patients with a history stable angina pectoris and / or MI. Of these, 57% had prior angina (and 78% had a history of MI). A total of 3090 patients were randomised to receive either bezafibrate (retard) or placebo and were followed up for a mean duration of 6.2 years. Treatment with bezafibrate did not confer any benefit over placebo for the primary endpoint of a composite of fatal MI, nonfatal MI and
sudden death. There was also no benefit observed for any of the individual
components of this endpoint. Bezafibrate had no benefit over placebo for the
following secondary endpoints: combination of hospitalisation for unstable angina,
percutaneous transluminal coronary angioplasty or coronary artery bypass graft,
hospitalisation for unstable angina, percutaneous transluminal coronary angioplasty,
coronary artery bypass graft, mortality, cardiac mortality, noncardiac mortality, stroke
or ischemic stroke.

Compared with the placebo group, triglyceride levels were lower in the bezafibrate
subgroup that had triglyceride levels ≥ 2.26 mmol/l. The overall incidence of any
adverse event was 69% in both groups, and the frequency of each type adverse
event was similar in both groups (Behar, S., Brunner, D., Kaplinsky, E. et al 2000).

Two randomised controlled trials were identified that compared fibrate therapy with
placebo in patients with a history of stroke or transient ischaemic attack (Acheson, J.
and Hutchinson, E. C. 1972) (Veterans Administration Cooperative Study Group.
1973). Both of these trials used clofibrate.

The first randomised controlled trial (Acheson, J. and Hutchinson, E. C. 1972)
recruited patients with focal cerebral vascular disease (those with one stroke,
multiple strokes or transient cerebral ischaemia) who had a serum cholesterol level
of 250 mg /100ml or higher. A total of 95 patients were randomised to receive either
clofibrate or placebo and the period of observation was from 4 months to 4 years.
Compared with placebo, clofibrate therapy was not associated with a decrease in all
cause mortality. Patients assigned to clofibrate had lower levels of serum
cholesterol compared to those who received placebo; mean proportional change in
serum cholesterol level was -12.69% for control and -21.41% for clofibrate (P <
0.05).

The second randomised controlled trial (Veterans Administration Cooperative Study
Group. 1973) recruited male veterans with one or more cerebral infarctions or
transient ischaemic attack within the past 12 months. A total of 532 men were
randomised to receive either clofibrate or placebo and were followed up for an
average duration of 21 months. Compared with placebo, clofibrate therapy was
associated with a non significant decrease in all cause mortality: 30/264 deaths
occurred in the placebo group versus 22/268 in the group allocated to receive clofibrate. For the outcome of vascular morbidity, there was no difference between the groups in the incidence of MI, TIA or angina. There was an increase in recurrence of cerebral infarction (23/264 placebo versus 37/268 clofibrate) and an increase in the incidence of congestive heart failure (4/264 placebo versus 15/268 clofibrate) in the clofibrate group compared to those receiving placebo but these differences were not tested for statistical significance. All other side effects were similar between groups. Regarding blood lipids, clofibrate decreased triglycerides compared to the control group (29% decrease clofibrate versus a 4% increase control) but had a negligible effect on cholesterol levels. Again, no statistical analysis was performed so the significance of these results is unknown.

One randomised controlled trial was identified that compared fibrate therapy with placebo in patients with a history of peripheral arterial disease (Meade, T. et al 2002). This trial recruited men with lower extremity arterial disease, 24% had stable angina, 21% had a previous MI and 12% had a history of stroke. A total of 1568 men were randomised to receive either bezafibrate (as Bezalip mono) or placebo and were followed up for a mean of 4.6 years. Bezafibrate therapy did not confer any benefit over placebo for the primary endpoint of a composite of CHD events (both fatal and non-fatal) and all strokes. When the individual endpoints were analysed separately, bezafibrate had no benefit over placebo for the primary outcome of a composite of CHD events and all strokes, but was associated with a reduction in the incidence of non-fatal CHD events (RR 0.60, 95% CI 0.36 to 0.99).

9.4.3 Cost effectiveness of fibrates

There were no cost effectiveness studies found on the use of fibrates compared with placebo in secondary prevention of CVD.

9.4.4 Evidence into recommendations

The GDG considered that there was insufficient evidence to routinely recommend the use of fibrates as a first line treatment for patients with CVD. It was decided however, that they may be offered as an alternative for those who are intolerant of statin therapy.
9.5 Nicotinic acids

9.5.1 Evidence statements for nicotinic acids

9.5.1.1 No randomised controlled trials were identified that compared nicotinic acid therapy with placebo in patients with angina, peripheral arterial disease or following stroke.

9.5.1.2 One randomised controlled trial in patients after MI found that nicotinic acid therapy was associated with a reduction in non-fatal MI and the combination of coronary death or non-fatal MI compared with placebo. Nicotinic acid therapy was not associated with a reduction in all cause mortality, cardiovascular mortality or cardiovascular morbidity compared with placebo.

9.5.2 Clinical effectiveness of nicotinic acids

No randomised controlled trials were identified that compared nicotinic acid therapy with placebo in patients with angina, peripheral arterial disease or following stroke. Due to the lack of trial evidence, it was decided by the GDG to consider evidence used in the NICE Myocardial Infarction guidance (Myocardial infarction - Secondary prevention in primary and secondary care for patients following a myocardial infarction, CG48, 2007).

One paper was identified that compared niacin treatment with placebo in patients after an MI (The coronary drug project research group 1975). The Coronary Drug Project Research Group randomly assigned post MI patients to six treatment groups: low and high conjugated oestrogen therapy, clofibrate, dextrothyroxine sodium, niacin and a placebo. The oestrogen and dextrothyroxine arms were stopped early because of an excess of nonfatal cardiovascular events and death, respectively.

Patients were followed for 5 years.

Compared with placebo, niacin was not associated with a reduction in the incidence of the following outcomes: all cause mortality, the individual components of all cause
mortality, definite pulmonary embolism (fatal or nonfatal), fatal or nonfatal stroke or inter­mittent cerebral ischaemic attack, definite or suspected fatal or nonfatal pulmonary embolism or thrombophlebitis and also any definite or suspected fatal or nonfatal cardiovascular event. Niacin therapy reduced the incidence of nonfatal MI and also the combination of coronary death or nonfatal MI, compared with placebo. Cholesterol and triglycerides levels decreased in the niacin group compared with the placebo group.

Patients in the niacin group had a greater incidence of the following side effects compared with the placebo group: the combination of diarrhea, nausea, vomiting, black tarry stools, stomach pain, flushing, itching of skin, urticaria, other type of rash, pain or burning when urinating, decrease in appetite, unexpected weight loss, and excessive sweating (The coronary drug project research group 1975).

9.5.3 Cost effectiveness of nicotinic acids
There were no cost effectiveness studies found on the use of nicotinic acids compared with placebo in secondary prevention of CVD.

9.5.4 Evidence into recommendations
The GDG considered that there was insufficient evidence to routinely recommend the use of nicotinic acids as a first line treatment for patients with CVD. It was decided however, that they may be offered as an alternative for those who are intolerant of statin therapy.
9.6 Anion exchange resins

9.6.1 Evidence statements for anion exchange resins

9.6.1.1 No randomised controlled trials were identified in patients with CVD that compared anion exchange resin therapy with placebo for the outcomes mortality or morbidity.

9.6.1.2 One small randomised controlled trial in patients with a history of CVD found that cholestyramine therapy was associated with a reduction in total cholesterol and LDL cholesterol compared with placebo.

9.6.2 Clinical effectiveness of anion exchange resins

No randomised controlled trials were identified in patients with CVD that compared anion exchange resin therapy with placebo for the outcomes mortality or morbidity. One small randomised controlled trial was identified on the clinical effectiveness of anion exchange resins compared with placebo to improve lipid level profiles in patients with coronary artery disease (Brensite, JF. 1984). This trial recruited people with elevated LDL cholesterol and angiographic evidence of coronary artery disease (50% of whom had symptomatic angina and / or MI). A total of 143 patients were randomised to receive either cholestyramine 24 g per day or placebo and were followed up for five years. Treatment with cholestyramine resulted in decreases in total and LDL cholesterol compared with placebo (5 year mean lipid level differences were - 0.1 mmol/l placebo versus - 1.4 mmol/l cholestyramine ($P < 0.001$) for total cholesterol and - 0.26 mmol/l placebo versus - 1.66 mmol/l cholestyramine ($P < 0.001$) for LDL cholesterol). Cholestyramine therapy did not have an effect on triglycerides or HDL cholesterol. There were negligible differences between groups for the ancillary outcomes of mortality and morbidity.

9.6.3 Cost effectiveness of anion Exchange Resins

There were no cost effectiveness studies found on the use of anion exchange resins compared with placebo in secondary prevention of CVD.
9.6.4 Evidence into recommendations

The GDG considered that there was insufficient evidence to routinely recommend the use of anion exchange resins as a first line treatment for patients with CVD. It was decided however, that they may be offered as an alternative for those who are intolerant of statin therapy.

9.7 Ezetimibe

9.7.1 Evidence statements for ezetimibe

9.7.1.1 Please refer to NICE Technology Appraisal No. XX ‘Ezetimibe for the treatment of primary (heterozygous familial and non-familial) hypercholesterolaemia’, (National Institute for Health and Clinical Excellence. 2007)

9.7.2 Clinical effectiveness of ezetimibe

The NICE Technology Appraisal XX entitled ‘Ezetimibe for the treatment of primary (heterozygous familial and non-familial) hypercholesterolaemia’, (National Institute for Health and Clinical Excellence. 2007) is currently being developed. The draft guidance recommends ezetimibe as a treatment option for primary (heterozygous familial and non-familial) hypercholesterolaemia and states that its recommendations should be read in the context of the lipid modification clinical guideline (this guidance).

The population groups covered by the ezetimibe Technology Appraisal XX (National Institute for Health and Clinical Excellence. 2007) are:

- Adults with primary (heterozygous familial and non-familial) hypercholesterolaemia who are candidates for treatment with statins on the basis of their CVD status or risk and;

- whose condition is not appropriately controlled with a statin alone or;

- in whom a statin is considered inappropriate or is not tolerated.
The term “not appropriately controlled with a statin alone” is defined as failure to achieve a target lipid level that is appropriate for a particular group or individual. It also assumes that statin therapy is optimised.

The NICE Technology Appraisal XX (National Institute for Health and Clinical Excellence. 2007) ‘Ezetimibe for the treatment of primary (heterozygous familial and non-familial) hypercholesterolaemia’ did not identify any randomised controlled trials that reported health-related quality of life or clinical endpoints such as cardiovascular morbidity and mortality; in the trials identified, surrogate outcomes such as total cholesterol, LDL cholesterol, HDL cholesterol and triglyceride levels were used as indicators of clinical outcomes.

To represent the population of people with hypercholesterolaemia that is not appropriately controlled with statin therapy, six 12-week fixed-dose randomised controlled trials (n = 3610) were identified that compared ezetimibe plus statin therapy with statin therapy alone.

Seven randomised controlled trials (n = 2577) comparing ezetimibe monotherapy with placebo represented the population where statin therapy is considered inappropriate or is not tolerated. All were 12-week studies and were included in a meta-analysis performed by the Assessment Group.

All trials involved people with primary hypercholesterolaemia with average baseline LDL cholesterol levels ranging from 3.4 mmol/litre to 6.5 mmol/litre and included mixed populations of people with and without a history of CVD.

9.7.3 Cost effectiveness of ezetimibe

The results of the cost effectiveness analysis carried out by the NICE Technology Appraisal (National Institute for Health and Clinical Excellence, 2007) will be adopted by this guideline.
9.7.4 Evidence into recommendations

Final recommendations of the NICE Technology Appraisal entitled ‘Ezetimibe for the treatment of primary (heterozygous familial and non-familial) hypercholesterolaemia’ will be adopted by this guideline.

9.8 Lipid measurement

9.8.1 Evidence statements for lipid measurement

9.8.1.1 Clinicians usually base treatment decisions on at least two laboratory measurements. LDL cholesterol is calculated indirectly using the Friedwald equation which depends upon a fasting triglyceride measurement. Direct measures are not yet routinely available in most laboratories. A baseline estimate of LDL cholesterol and triglycerides is considered to provide further information on cardiovascular risk.

9.8.2 Lipid measurement – evidence to recommendations

The GDG considered the number and type of lipid measurements. Estimates of ‘true’ lipid levels will be more precise from multiple samples than from single samples. In routine practice these statistical considerations are tempered by pragmatic issues of feasibility and convenience. When initiating lipid modifying therapy most clinicians regard a minimum of at least two estimates of lipids as useful and practicable of which one should be fasting in order to provide an accurate measure of triglycerides and an indirect measure of LDL cholesterol. Direct methods are available but are not routinely available in many laboratories. After an acute coronary event, lipid metabolism is disturbed and measurement at this time is not advised. Treatment should not be delayed and measurement can be delayed to around 3 months after the event.

The GDG concurred with this view and recommended a fasting specimen should be obtained prior to treatment. The GDG also agreed that in people who have recently experienced an acute coronary event later estimation within three months of the event, may be preferable (Carlsson, R. et al 1995; (Ryder, R. E. et al 1984).
Routine lipid monitoring is discussed in section 4.3.7.2

10 Appendices A–J (these are available in a separate file)

Appendix A – Audit Criteria
Appendix B – Scope
Appendix C – Health Economic Modelling
Appendix D – Clinical Evidence Extractions
Appendix E – Health Economic Extractions
Appendix F - Clinical Questions and Search Strategy
Appendix G – Omega-3 fatty acids content of various oily fish required to provide approximately 1 g of EPA plus DHA per day
Appendix H – Recommended Framingham risk equations definitions and coefficients
Appendix I – Strategies for identification of patients at high risk of CVD in primary care
Appendix J – A systematic review of risk scoring methods and clinical decision aids used in the primary prevention of coronary heart disease

11 Reference List


(7) National Institute for Health and Clinical Excellence. Four commonly used methods to increase physical activity: brief interventions in primary care, exercise referral schemes, pedometers and community-based exercise programmes for walking and cycling. England: NICE. 2007


(70) Hense HW, Schulte H, Lowel H, Assmann G, Keil U. Framingham risk function overestimates risk of coronary heart disease in men and women from
Germany--results from the MONICA Augsburg and the PROCAM cohorts.
European Heart Journal 2003; 24(10):937-945.

(71) Hetlevik I, Holmen J, Kruger O. Implementing clinical guidelines in the
treatment of hypertension in general practice. Evaluation of patient outcome
related to implementation of a computer-based clinical decision support

(72) Hetlevik I, Holmen J, Kruger O, Kristensen P, Iversen H. Implementing clinical

(73) Hjerkinn EM, Sandvik L, Hjemmerv I, Arnesen H, Hjerkinn EM, Sandvik L,
Hjemmerv I, Arnesen H. Effect of diet intervention on long-term mortality in

(74) Hjemmerv I, Velve BK, Holme I, Leren P, Hjemmerv I, Velve Byre K, Holme I,
Leren P. Effect of diet and smoking intervention on the incidence of coronary
heart disease. Report from the Oslo Study Group of a randomised trial in

(75) Jensen GB, Hampton J. Early termination of drug trials. BMJ 2007;
334(7589):326.

(76) Jones PH, Hunninghake DB, Ferdinand KC, Stein EA, Gold A, Caplan RJ,
Blasetto JW. Effects of rosuvastatin versus atorvastatin, simvastatin, and
pravastatin on non-high-density lipoprotein cholesterol, apolipoproteins, and
lipid ratios in patients with hypercholesterolemia: additional results from the

lowering by pravastatin on progression and regression of coronary artery
disease in symptomatic men with normal to moderately elevated serum
cholesterol levels. The Regression Growth Evaluation Statin Study

Effects of long-term fenofibrate therapy on cardiovascular events in 9795
people with type 2 diabetes mellitus (the FIELD study): randomised controlled

(79) LaRosa JC, Grundy SM, Waters DD, Shear C, Barter P, Fruchart JC, Gotto
AM, Greten H, Kastelein JJP, Shepherd J, Wenger NK. Intensive lipid
lowering with atorvastatin in patients with stable coronary disease. New
(80) Law M, Rudnicka AR. Statin safety: a systematic review. Am J Cardiol 2006; 97(8A):52C-60C.


(103) Nilsson PM, Nilsson JA, Berglund G. Family burden of cardiovascular mortality: risk implications for offspring in a national register linkage study


Quirke TP, Gill PS, Mant JW, Allan TF. The applicability of the Framingham coronary heart disease prediction function to black and minority ethnic groups in the UK. Heart 2003; 89(7):785-786.


cardiac events following successful first percutaneous coronary intervention: a

(125) Serruys PW, Foley DP, Jackson G, Bonnier H, Macaya C, Vrolix M, Branzi A,
Shepherd J, Suryapranata H, de Feyter PJ, Melkert R, van Es GA, Pfister PJ.
A randomized placebo-controlled trial of fluvastatin for prevention of
restenosis after successful coronary balloon angioplasty; final results of the
fluvastatin angiographic restenosis (FLARE) trial. European Heart Journal

The lifetime risk of stroke: estimates from the Framingham Study. Stroke

(127) Sesso HD, Lee IM, Gaziano JM, Rexrode KM, Glynn RJ, Buring JE. Maternal
and paternal history of myocardial infarction and risk of cardiovascular

(128) Sever PS, Dahlof B, Poulter NR, Wedel H, Beevers G, Caulfield M, Collins R,
Kjeldsen SE, Kristinsson A, McInnes GT, Mehlisen J, Nieminen M, O’Brien E,
Ostergren J, ASCOT investigators. Prevention of coronary and stroke events
with atorvastatin in hypertensive patients who have average or lower-than-
average cholesterol concentrations, in the Anglo-Scandinavian Cardiac
Outcomes Trial–Lipid Lowering Arm (ASCOT-LLA): a multicentre randomised

(129) sheikh-Ali AA, Ambrose MS, Kuvjin JT, Karas RH. The safety of rosuvastatin
as used in common clinical practice: a postmarketing analysis. Circulation

(130) Shepherd J, Blauw GJ, Murphy MB, Bollen EL, Bucklen BM, Cobbe SM, Ford
I, Gaw A, Hyland M, Jukema JW, Kamper AM, Macfarlane PW, Meinders AE,
Norrie J, Packard CJ, Perry IJ, Stott DJ, Sweeney BJ, Twomey C,
Westendorp RG, PROSPER study group. Pravastatin in elderly individuals at
risk of vascular disease (PROSPER): a randomised controlled trial. Lancet
2002; 360(9364):1623-1630.

(131) Shepherd J, Cobbe SM, Ford I, Isles CG, Lorimer AR, Macfarlane PW,
McKillop JH, Packard CJ. Prevention of coronary heart disease with
pravastatin in men with hypercholesterolemia. West of Scotland Coronary

(132) Sheridan S, Pignone M, Mulrow C. Framingham-based tools to calculate the
global risk of coronary heart disease: a systematic review of tools for

(133) Silva MA, Swanson AC, Gandhi PJ, Tataronis GR. Statin-related adverse


(138) Tonkin AM ESW. Cost-effectiveness of cholesterol-lowering therapy with pravastatin in patients with previous acute coronary syndromes aged 65 to 74 years compared with younger patients: results from the LIPID study. Am Heart J 2006; 151(6):1305-1312.


